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EPIPHORA

IMPACT ON VISION, OUTCOME OF LACRIMAL SURGERY AND INVESTIGATIONS WITH ULTRA-HIGH-FREQUENCY ULTRASOUND

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Epiphora – Impact on vision, outcome of lacrimal surgery and investigations with ultra-high-frequency ultrasound
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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To my mother Christina and my son Gabriel –

I love you both with all my heart.

THESIS AT A GLANCE

	Research question	Subjects and methods	Results	Conclusion
I	Do patients with ALDO experience more or less visual disability than cataract patients?	Comparison of Catquest-9SF answers from 72 patients with ALDO and 3625 patients awaiting cataract surgery	Rasch scores for ALDO patients and second- eye cataract patients were equivalent.	Patients with ALDO experience similar visual disability to patients waiting for cataract surgery in their second eye.
II	What is the current practice for managing ALDO in the Nordic countries?	Online survey answered by 51 ophthalmological clinics in the five Nordic countries	-Treatment follows standard care, except that CDCP is more favored. -Frustration that demand exceeds resources.	In the Nordic countries there are challenges regarding surgical training and the provision of lacrimal surgery.
III	How successful is CDCP in the long-term in the treatment of ALDO, and does the location of stenosis matter?	87 cases of ALDO in 72 patients treated with CDCP were followed for 76 months.	The reoperation rate was significantly higher in NLDO/ multiple stenosis than in canalicular stenosis.	CDCP may not be an adequate alternative when treating complete NLDO.
IV	What is the long-term success rate of DCR if the silicone stent is only retained for a very short time?	70 cases of uncomplicated DCR with one-week intubation in 67 patients were followed for 4 years.	The long-term functional or anatomical success rate was 97%.	A high long-term success rate for uncomplicated DCR is possible with only one-week silicone stent intubation.
V	How does the lacrimal sac move during a blink cycle?	-The upper lacrimal drainage system was investigated with 40-70 MHz ultrasound in 22 eyes. -Motion tracking was used to map movement.	The direction of motion of the lateral lacrimal sac wall is mainly in the anterior-posterior direction during blinking, in contrast to previous theories.	Findings suggest that current theories of active tear drainage need to be reappraised.

POPULÄRVETENSKAPLIG SAMMANFATTNING

En vanlig missuppfattning är att rinnande ögon inte är något stort problem för de personer som drabbas. Vi som möter dessa patienter får dock höra beskrivningar av problem med tårar som trillar ned på tangentbordet under arbetet eller berättelser om barnbarnen som frågar varför mormor är ledsen. Huden på ögonlocken kan bli röd och eksematös av allt torkande och av att alltid vara fuktig. Tårfilmen är dessutom den första yta som ljuset träffar när det når ögat och ett överskott av tårar gör att den blir oregelbunden och hela tiden varierar sin brytande förmåga vilket ger en sämre syn. Man kan jämföra med den suddiga bild man får när man tittar ut genom en blöt fönsterruta. Dessa problem är vanligtvis mer uttalade vid blick nedåt då man tittar genom den tjockare tårmenisken som ligger innanför det nedre ögonlocket. Detta ger problem vid läsning, handarbete och annat närarbete, när man går nedför trappor eller på ojämnt underlag. När synskärpa testas hos en optiker eller ögonläkare är man inomhus och patienten tillåts blinka och torka ur ögonen vilket gör att man ofta uppmäter normal syn och då missar de problem som finns i vardagen. Detta bidrar förmodlighet till att problem med tårflöde får mycket lite uppmärksamhet och inte prioriteras inom den svenska sjukvården.

I den här avhandlingen undersöker vi vilken grad av problem tårflöde kan ge, hur vi behandlar stopp i tårkanalerna och vad våra behandlingar har för resultat på sikt. Slutligen tittar vi även på en del av den pumpfunktion som får tårarna att rinna bort från ögat. Samtliga studier rör enbart tårflöde orsakade av tårvägshinder eller nedsatt pumpfunktion hos vuxna då barn har andra orsaker till tårvägsbesvär och behandlas på annat sätt.

I det svenska nationella kataraktregistret har man länge använt sig av förbättring av upplevd synförmåga som ett mått på hur bra kataraktoperationer är. Nedsättning av upplevd synförmåga definieras som hur mycket hinder en person upplever i vardagen på grund av problem med synen och för att mäta detta har man tagit fram ett formulär som heter Catquest-9SF. I första studien har vi bett patienter med tårflöde orsakat av stopp i tårkanalerna svara på samma formulär. Vi har kunnat visa att tårvägspatienters besvär i vardagen är ungefär lika stora som de patienter som är kataraktopererade på ett öga och som väntar på operation i andra ögat. Att få bli kataraktopererad på båda ögonen om man har problem är självklart i Sverige men inte att bli omhändertagen om man har stopp i tårvägarna.

För att få en kartläggning av hur vi i dag undersöker och behandlar vuxna med rinnande ögon har vi i en andra studie skickat ett frågeformulär till de ögonkliniker som erbjuder tårvägskirurgi i de nordiska länderna. Vi frågar bland annat vad de skulle välja för operation vid olika typer av stopp i tårvägarna. 65 % av de tillfrågade klinikerna svarade på formuläret och i stort följer valda operationer de allmänt accepterade behandlingsstrategierna. Ett undantag är dock att man gärna väljer att sondera och lägga ned en silikonslang som ett första steg hos patienter med stopp nedanför tårsäcken. Få studier har tittat på hur bra det fungerar och de som finns är antingen små eller har kort uppföljningstid. I sista frågan i frågeformuläret ombads de som svarade säga vad de upplevde som den största svårigheten när det kommer till att behandla tårflöde och tårvägssjukdomar. Generellt uttrycktes en frustration över att det var många fler som sökte för tårflöde än vad man med tillgängliga resurser klarade att ta hand om.

Eftersom sondering och silikonslangsnedläggning är ett vanligt ingrepp i Norden trots att det finns få studier så valde vi i den tredje studien att titta på hur många som efter ingreppet fick tillbaka sitt stopp och behövde opereras om. Vi undersökte även om frekvensen skiljde sig åt beroende på var i tårvägarna stoppet satt. Efter drygt 6 år hade 39% av patienterna behövt bli opererade igen. Risken för att få tillbaka stoppet och behöva bli omopererad var signifikant högre om stoppet satt nedanför tårsäcken eller om man hade flera stopp än om stoppet bara satt i kanaliklarna (de mindre tårvägarna mellan tårpunkt och tårsäck). Problemet är dock att det är först under operationen som man med säkerhet kan säga att stoppet bara sitter ovanför tårsäcken. Om man däremot kan säga att det finns ett stopp nedanför tårsäcken så är sondering och silikonslangsnedläggning inget bra alternativ.

Bland tårvägskirurger så debatteras om man ska lägga in en silikonslang i samband med en DCR operation (skapande av ny kanal mellan tårsäck och näsan). De studier där man undersökt detta har rapporterat väldigt blandade resultat. Det man dock inte tagit hänsyn till är hur länge man låter silikonslangen ligga kvar efter operationen och detta varierar mycket mellan studier. En av anledningarna till att tiden varierar så mycket är att man inte är säker på vilken effekt silikonslangen har. En teori är att silikonslangen gör nytta bara de första dagarna genom att leda bort sårvätska och sekret. Man vet också att silikonslangar kan ge komplikationer i form av ärrgranulom (ofarliga ärrpolyper), skav och uttänjda tårpunkter. Vi kan i fjärde studien visa att det är möjligt att ha mycket lyckade operationsresultat med en så kort slangtid som en vecka i okomplicerade fall. Detta är en kortare slangtid än vad som tidigare rapporterats och vi presenterar i artikeln iden att det finns ett tidsfönster där slangen gör nytta men om den får sitta längre så riskerar den att bidra till att resultatet av operationen blir sämre.

I sista och femte studien har jag samarbetat med ögonkliniken i Lund. Där finns möjlighet att undersöka patienter med ultrahögfrekvent ultraljud, upp till 70MHz, och detta har vi använt för att kartlägga övre delen av tårkanalsystemet samt titta på hur tårsäcken rör sig under blinkning. Vi kan visa att tårsäckens vägg framförallt rör sig parallellt med benet och inte vinkelrätt mot det som tidigare har beskrivits. Detta innebär att tidigare teorier om hur tårpumpen fungerar kan behöva revideras. Vårt fynd ger också visst stöd till den teori som säger att tårsäcken “vrids ur” vid varje blinkning och tårarna på så sätt pumpas in i tårkanalen och vidare till näsan.

Sammanfattningsvis så kan vi i den här avhandlingen presentera fynd som tyder på att tidigare teorier om det aktiva tårdränaget inte helt stämmer. Att det är möjligt att med en mycket kort slangtid få ett mycket bra operationsresultat för DCR:er. Att vi i de nordiska länderna bör överväga att minska användningen av sondering och silikonslangsnedläggning för att behandla stopp nedom tårsäcken. Framförallt bör de som prioriterar inom ögonsjukvården inse att tårflöde kan vara mycket besvärligt om det är uttalat, så till den grad att det påverkar det dagliga livet.

ABSTRACT

Epiphora is a common condition that often receives little attention. Excessive tear production creates an irregular and ever-changing ocular surface, affecting refraction and reducing vision. However, in a standard test situation the visual acuity is seldom affected, leading to the misinterpretation that epiphora is a minor problem. Patients report social discomfort as a result of red eyes and constant eye wiping, and the misperception that they are sad or crying.

The aims of the present studies were to quantify the functional visual disability experienced by patients with epiphora, to survey current management practices, and to present the long-term outcome of two lacrimal drainage procedures. In addition, a novel imaging technique, ultra-high-frequency (UHF) ultrasound, was used to visualize the upper lacrimal drainage anatomy and the lacrimal pump.

Limitations on activities in daily life due to visual disability have long been recorded in the Swedish National Cataract Register and used as an outcome measure. The tool used, a questionnaire named Catquest-9SF, was validated in this study for epiphora patients, and their visual disability was found to be in parity with those of patients awaiting cataract surgery in their second eye (Paper I).

A survey of current management practices in the Nordic countries regarding acquired lacrimal drainage obstruction (ALDO) indicated that canaliculodacryocystoplasty (CDCP) is used when treating obstructions below the lacrimal sac (Paper II), a practice less common elsewhere. However, approximately half of patients with multiple obstructions or nasolacrimal duct obstructions (NLDO) treated with CDCP require additional surgery due to the recurrence of obstruction (Paper III). This proportion is significantly higher than when stenosis is confined to the canaliculi.

There is no consensus regarding the use of silicone stent intubation in conjunction with dacryocystorhinostomy (DCR). The duration of intubation has received little attention as a factor contributing to outcome. A 97% long-term success rate was found with a comparatively short intubation duration of one week (Paper IV). This shows that a high success rate is possible with a one-week intubation period. I suggest that there may be an optimal duration of intubation, with which the possible positive effects are achieved while the negative effects minimized.

Using UHF ultrasound and motion tracking, it was demonstrated that the motion of the lateral lacrimal sac wall is greatest in the anterior-posterior direction during blinking (Paper V). This is in contrast to an existing theory regarding the mechanics of the lacrimal pump.

In conclusion, the findings presented in this thesis suggest that epiphora should be recognized as a debilitating condition affecting everyday life, and that the use of CDCP to treat NLDO should be reconsidered in the Nordic countries, as it may be an inadequate form of treatment. Furthermore, a very high success rate is possible with a short duration of intubation in DCR. Finally, the current theory regarding the lacrimal pump should be re-evaluated.

LIST OF SCIENTIFIC PAPERS

I. Bohman E, Wyon M, Lundstrom M, Dafgard Kopp E. A comparison between patients with epiphora and cataract of the activity limitations they experience in daily life due to their visual disability. Acta Ophthalmol. 2018; 96: 77-80

II. Bohman E, Roos JCP, Kopp ED. The first large pan-Nordic survey of the management of acquired lacrimal drainage obstruction in adults. J Clin Exp Ophthalmol 2019; 10: 793

III. Bohman E, Kugelberg M, Dafgård Kopp E. Long-term outcome of lacrimal stent intubation for complete acquired lacrimal drainage obstructions. Acta Ophthalmol. 2020; 98: 396-99

IV. Bohman E, Dafgård Kopp E. One-week intubation in external dacryocystorhinostomy - a report on long-term outcome. Orbit. 2020 [Epub ahead of print]

V. Bohman E, Berggren J, Bunke J, Albinsson J, Engelsberg K, Dahlstrand U, Hult J, Hasegawa H, Cinthio M, Sheikh R. Novel evidence concerning lacrimal sac movement using ultra-high-frequency ultrasound examination of lacrimal drainage systems. Ophthalmic Plast Reconstr Surg. 2020 [Epub ahead of print]

CONTENTS

LIST OF ABBREVIATIONS

ALDO	Acquired Lacrimal Drainage Obstruction
CDCP	Canaliculodacryocystoplasty
DCR	Dacryocystorhinostomy
NLDO	Nasolacrimal Duct Obstruction
PANDO	Primary Acquired Nasolacrimal Duct Obstruction
PROM	Patient-Reported Outcome Measure
SALDO	Secondary Acquired Lacrimal Drainage Obstruction
UHF	Ultra-High Frequency

1 INTRODUCTION

“It’s nothing, just a watery eye”

Imagine trying to see the price tag in a store, but your eyes are so watery that it is almost impossible. Picture cycling to work on a sunny day and arriving with a wet face, or trying to read the newspaper while tears fall on the text. You constantly feel that you are looking through a wet window. When you finally go to the doctor, he or she says, “Don’t worry, your eyesight is perfect. You just have a watery eye”. Within the field of oculoplastic surgery, I have met few patients who felt more misunderstood than those with epiphora. In addition, I have met few more grateful patients than those with lacrimal obstructions in whom dacryocystorhinostomy has been successful. This is what motivates me to expand my understanding of this condition.

Epiphora in children and adults have different etiologies with the exception that traumatic obstructions may affect both. In congenital lacrimal obstruction, epiphora is due to incomplete development of the lacrimal drainage system and the treatment is quite straightforward once the extent of the dysgenesis has been established.[1] In adults, a number of different etiologies may cause epiphora and much less is known about the pathological processes. Often, the exact cause cannot be established, making the decisions regarding treatment much more complex. In this work, different aspects of epiphora in adults were investigated in an attempt to address the following questions: How much of a problem is a constantly tearing eye? How do we currently treat patients with epiphora? Should we treat these patients differently in the future? For example, is there anything we could improve regarding the indications for lacrimal surgery or surgical techniques? Finally, is it possible to increase our knowledge about the active drainage of tears using the latest imaging techniques?

2 EPIPHORA

A non-psychological excess of tears can be caused by either lacrimation or epiphora. Lacrimation is increased tear production (reflex tearing) due to ocular irritation such as reduced tear quality, surface disease, inflammation, entropion or trichiasis. Epiphora, on the other hand, is impaired function of the lacrimal drainage apparatus caused by: 1) malposition of the puncta, 2) complete or partial stenosis, or 3) dysfunction of the active tear drainage.[2]

2.1 TEAR DRAINAGE

It is generally accepted that tear drainage is an active process, and not the passive flow of tears through the lacrimal drainage system (Figure 1). Several theories for tear drainage have been proposed, but the exact mechanism is not yet fully understood.[3]

The lacrimal pump theory involves the action of the medial retinaculum on the canaliculi and lacrimal sac during the blink cycle, creating alternating compression and distension, forcing the tears forward.[4-8] This theory is sometimes divided into the "lacrimal sac pump theory" and the "canalicular pump theory". The medial retinaculum is a complex system of muscle fibers and tendons, for example, the pars lacrimalis of the orbicularis oculi muscle, also called Horner's muscle, surrounding the canaliculi and the lacrimal sac in the medial canthal area.[7, 9] It has been theorized that during eyelid closure the lacrimal sac distends upwards while the lateral wall is pushed out medially. In contrast, when opening the eyelid, the apex of the lacrimal sac is pushed downwards and the lateral wall pulled laterally.[6]

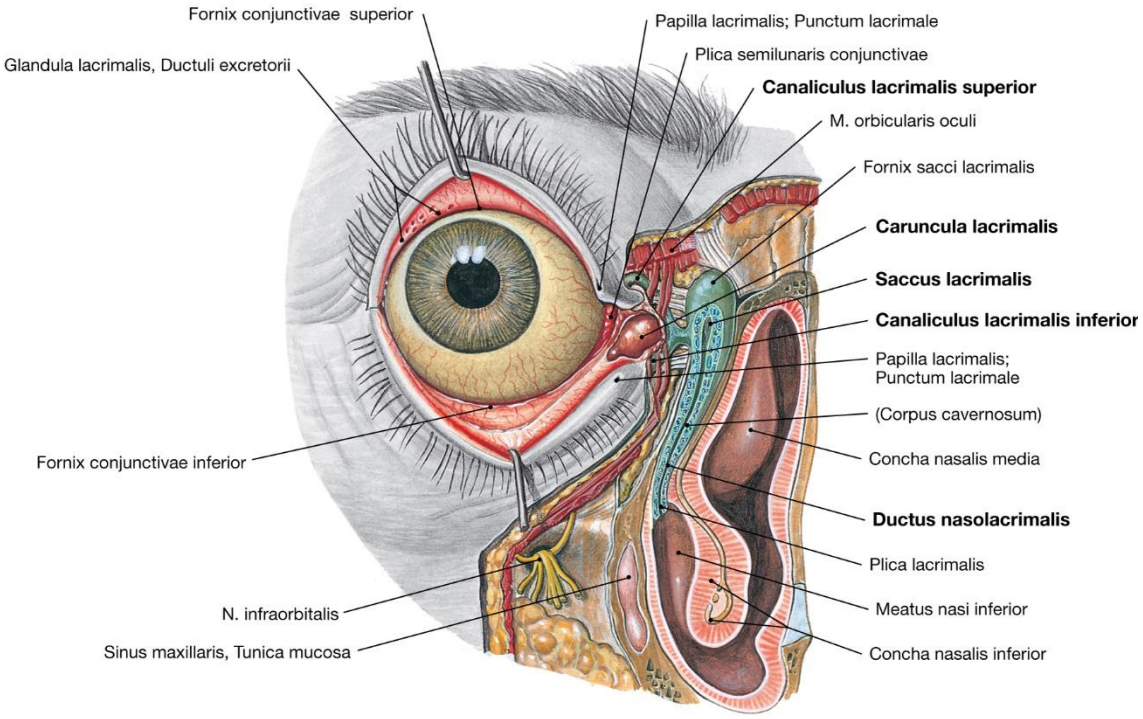
The lacrimal sac and lacrimal duct are surrounded by a vascular plexus, which may play a role in the regulation of tear flow (Figure 1).[10, 11] The vasculature consists of highly specialized vessels with the ability to control their distention and contraction, and thus the lumen of the lacrimal duct, as shown by Paulsen et al. in a series of studies.[10, 12, 13] There is evidence that the vessels have neural innervation, and that regulation is partly controlled by a neural reflex loop from the cornea.[3, 12]

Between the vessels in the vascular plexus are helically arranged collagen fibers. The "wrung out" theory postulates that during blinking the lacrimal sac is distended vertically and, as a result, the lacrimal sac lumen is narrowed by passive twisting squeezing caused by the collagen fibers, expelling tears into the lacrimal duct.[11]

It has also been proposed that tears are actively reabsorbed into the vascular plexus.[14] This theory is supported by the fact that a number of different aquaporin proteins, a group of proteins important for water transportation across plasma membranes in many organs, have been found in the lacrimal sac and duct.[15]

Other mechanisms have been suggested for the active drainage of tears, such as capillary forces, the Venturi effect caused by breathing, and the action of gravity, but none has been adequately confirmed.[16]

A



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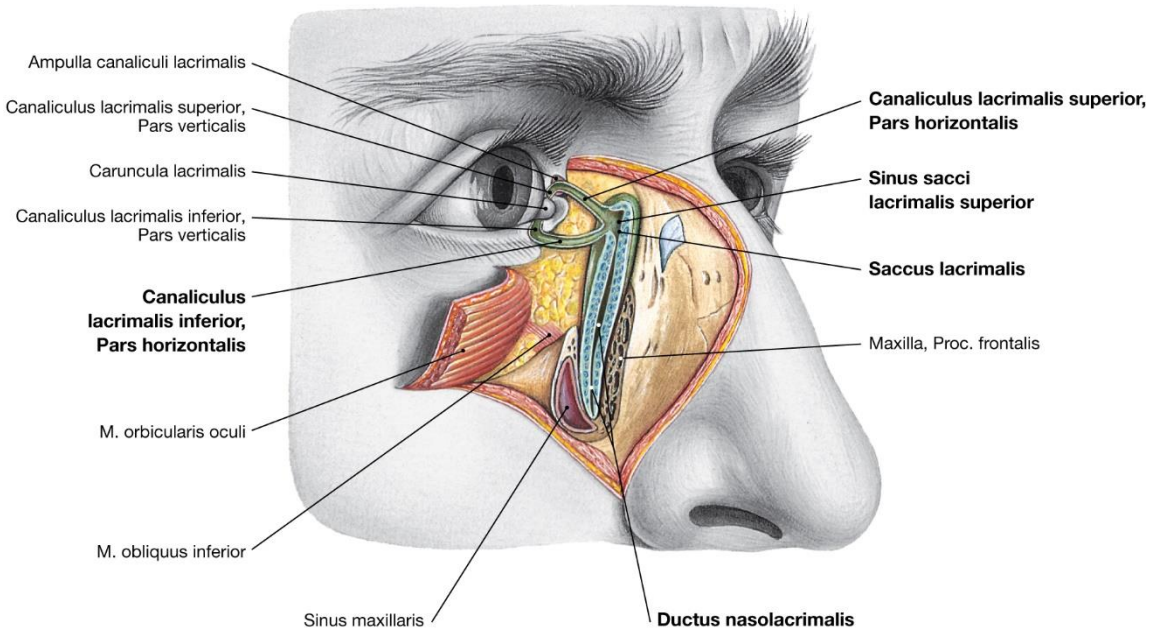

Figure 1: Anatomy of the right lacrimal drainage system illustrating the complex relationship between the structures in the medial canthal area. The location of the highly specialized vascular plexus can also be seen. A) Frontal view, B) lateral view.
Reproduced with permission from Paulsen, Waschke, Sobotta Anatomy Textbook, 1st Edition 2018, © Elsevier GmbH, Urban & Fischer, Munich.

At first glance, these theories may seem contradictory, especially the lacrimal pump theory and the "wrung out" theory, as they appear to suggest different movements of the lacrimal sac. However, they might not be mutually exclusive. It must be borne in mind that the above-mentioned theories are based on histological or electron microscopic examinations, cadaver dissections, pressure measurements and/or non-physiological imaging methods, and that different aspects of the active drainage mechanism may be revealed depending on the method used. Moreover, peristaltic-like movements, neural innervation and tear reabsorption may represent complementary regulatory systems acting in different time frames. For example, the mechanical pump function could provide basal drainage, and neural innervation may be responsible for fast-acting regulation, while tear reabsorption could either be part of the basal drainage or play a part in slow-acting modulation.

Establishing the true *in vivo* mechanisms controlling tear drainage is important as they provide the basis for further research into the pathophysiology of primary acquired lacrimal stenosis. It would also help to improve our understanding of "functional epiphora", which is believed to be caused by dysfunction of the active tear drainage.

2.2 EPIDEMIOLOGY OF LACRIMAL OBSTRUCTIONS

Despite many publications in which it is stated that epiphora is a very common problem, there are surprisingly few studies on the incidence and prevalence of acquired lacrimal duct obstruction (ALDO).

In a large study, Woog et al. reported the overall incidence rate of symptomatic ALDO to be 30/100 000 person years, with nasolacrimal duct obstruction (NLDO) being the most common form of stenosis, with an incidence rate of 20/100 000 person years.[17] The majority of participants in the study were women (69%), and the proportion was even higher among patients with NLDO (73%). In addition, they found an increase in incidence rate with age, with a slow increase starting at 40 years of age, and increasing more rapidly from the age of 60.

The results presented by Woog et al. are in line with those of two smaller studies on the prevalence of ALDO at tertiary oculoplastic centers. In these smaller studies, slightly less than half of the patients referred for watery eyes had ALDO, and the female:male ratio was between 2.3:1 and 6.9:1.[18, 19] Furthermore, the age and gender distributions correlated well with those reported in numerous studies on lacrimal surgery.[20-23]

It can therefore be concluded that ALDO is indeed very common, with a predisposition among women, and increasing with age (Figure 2).

Figure 2: The most common patient affected by ALDO is a female over 60 years of age. Photo: Elin Bohman

2.3 PATIENTS' SYMPTOMS AND COMPLAINTS

The first optical surface that light encounters when entering the eye is the tear film, and its stability and uniformity are important in maintaining high optical quality. Excess tear production, whether from lacrimation or epiphora, causes the tear film to vary, resulting in blurred vision, comparable to looking through a wet window. This blurring tends to increase when looking down as the thickness of the tear meniscus is greater, leading to problems when reading, writing, cooking, negotiating stairs or doing fine work.[24] In addition, contrast sensitivity is reported to be significantly reduced in patients with ALDO, possibly due to increased light scattering from proteins in the tear film.[25] Aberrations have been found to decrease after lacrimal surgery, with less fluctuation over time, accompanied by an increase in functional visual acuity.[26] However, visual acuity is rarely affected in traditional eye-test situations, as the patients are allowed to wipe their eyes and blink until their view becomes clear.[25] Cataracts, corneal dystrophies and other more static problems affecting the visual axis may lead to some degree of tolerance that is not achieved in a watery eye where refraction changes rapidly.[27] This may explain why there is evidence that unilateral epiphora affects the quality of life as much as bilateral problems.[27]

If the obstruction is in the lower part of the lacrimal sac or the nasolacrimal duct, tears collect in the sac creating a mucocele. This leads to discomfort resulting from distension of the sac, and the patient may feel the need to repeatedly massage the area to press out the clear gelatinous mucus. Even if not actively compressed, some reflux may occur, resulting in the feeling of a sticky eye.[28] A lacrimal sac mucocele is also the perfect site for chronic or acute dacryocystitis with the potential risk of preseptal or orbital spread.[29] In addition to the before-mentioned symptoms, patients with epiphora often complain of dry or eczematous periocular

skin and spattered glasses, as well as having the social embarrassment of a constantly weeping eye or the appearance of crying.[24]

2.4 ETIOLOGY AND PATHOPHYSIOLOGY

There are several known etiologies of ALDO, often referred to as “secondary causes” or secondary acquired lacrimal drainage obstructions (SALDO), as opposed to “primary” or “idiopathic” obstructions (Figure 3). Primary canalicular stenosis is quite rare, and in many cases a secondary cause can be found, in contrast to acquired NLDO, where the majority of cases are idiopathic (primary acquired nasolacrimal duct obstruction (PANDO)).[30] Epiphora may exist despite anatomical patency, and is often referred to as “functional epiphora”.

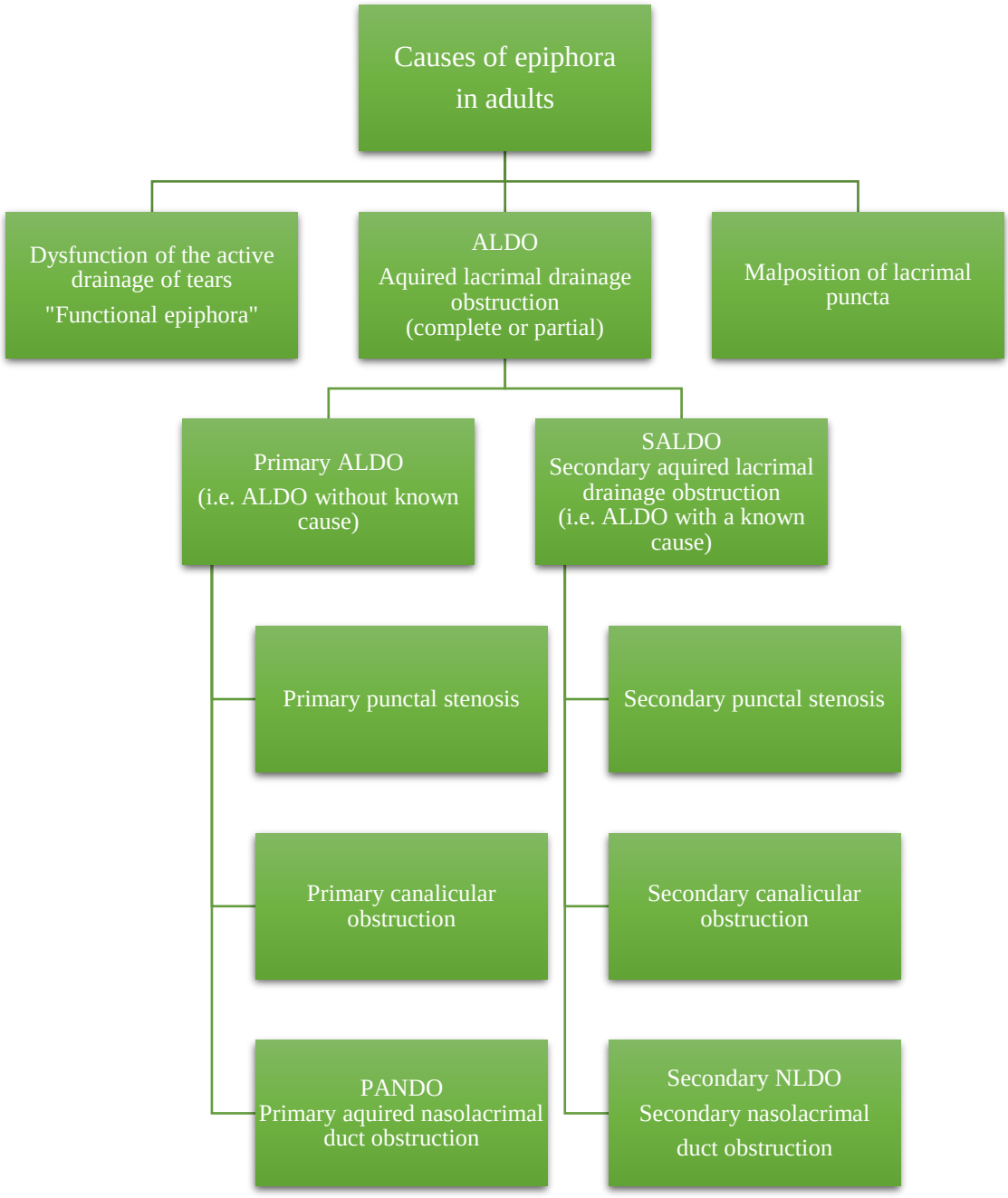

Figure 3: Relation between different causes of epiphora in adults.

2.4.1 Primary acquired nasolacrimal duct obstructions

A major breakthrough in the understanding of the pathogenesis of PANDO came with Lindberg and McCormic's study in 1986. They developed a biopsy technique for the nasolacrimal duct, and found three different stages of inflammation that were correlated with the duration of symptoms and severity of disease.[31] The first was an active inflammation stage, with edema of the periductal tissues and infiltration of lymphoplasmacytic cells. The second was an intermediate stage with chronic inflammation and focal signs of fibrotic obliteration, while the third was a fibrotic stage with complete fibrous obliteration of the nasolacrimal duct lumen. Paulsen et al. later confirmed these findings.[32] However, it is still not known what causes inflammation in the first place.

Several factors have been suggested to contribute to the formation of PANDO and to explain its predominance among women. Ali and Paulsen summarized the currently proposed mechanisms in a major review.[33] They concluded that there was no convincing evidence for the contributions of anatomical factors, sino-nasal factors, gastroesophageal reflux, lysosomal dysregulation or miscellaneous factors (e.g. make-up, swimming-pool exposure, glaucoma medication or smoking). There was some evidence suggesting that vascular factors and autonomic dysregulation may play a role, as well as antimicrobial defense and infections, but no mechanisms have yet been identified. In a recent study, it was found that an altered sino-nasal microbiome was associated with PANDO, but it is not certain whether this is a cause or a consequence.[34]

Prolactin and prolactin-inducible protein has been suggested to play a role in the development of PANDO, and high levels have been found in the lacrimal sac and duct.[35] Among other functions, prolactin has cytokine-like properties and modulates inflammatory response, and if it is involved in the pathogenesis of PANDO, this could explain the predominance in postmenopausal females. Some studies have been published recently showing altered expression of surfactant proteins in the epithelium of the lacrimal drainage system in patients with PANDO.[36, 37] In the alveoli of the lungs, this group of proteins is responsible for reducing surface tension and preventing collapse, but it is not known whether they have a similar role in the lacrimal sac and duct.

In summary, although some light has been shed on the development of PANDO, allowing some factors to be excluded and others to be revealed, much is still unknown. When primary stenosis is established, the exact mechanism of its formation will probably not alter the choice of treatment or affect the outcome. However, improved knowledge on the pathophysiology may provide targets for future treatments that inhibit stenosis formation altogether.

2.4.2 Secondary acquired lacrimal drainage obstructions

Bartley proposed, and published in tree parts, a classification system for secondary causes in the 1990s that is still valid today as a systematic framework, although some causes have since been questioned, and others added.[38-43] Table 1 provides an updated summary of this classification system.

Due to the risk of an unknown secondary cause, especially neoplasia, the question of routine biopsy during surgery has been raised. The incidence of an unexpected cause is reported to be around 3% in large dacryocystorhinostomy (DCR) series; the most common being inverted papilloma, oncocytoma, dacryolith and granuloma.[44, 45] If the lacrimal sac appears normal when inspected intraoperatively, biopsy is not indicated. In contrast, if a mass is found, or the lacrimal sac epithelium has an abnormal appearance biopsy is advisable. Suspicion should be higher in male patients as the incidence of PANDO is lower in this group.[30] It has also been shown that the risk of a secondary cause is twice as high when there is bilateral obstruction, and that this risk increases further if the patient is younger than 50 years of age.[46]

Table 1: Summary of the updated Bartley classification system for secondary causes of lacrimal obstruction

Class	Subclass	Example
Infectious	Bacterial	*Actinomyces* spp., *Chlamydia trachomatis*
	Viral	*Herpes simplex, Herpes zoster, Adenovirus*
	Fungal	*Aspergillus*
Inflammatory	Endogenous	Granulomatous polyangiitis, sarcoidosis, cicatricial pemphigoid, Stevens–Johnson syndrome
	Exogenous	Chemotherapy (for example, docetaxel), radiation treatment, graft-versus-host disease, pseudopemphigoid
Neoplastic	Primary	Papilloma, inverted papilloma, oncocytoma
	Secondary	Basal cell carcinoma, squamous cell carcinoma
	Metastatic	Breast cancer, malignant melanoma, prostate cancer
Traumatic	Iatrogenic	Punctal occlusion for dry eye, secondary to probing
	Non-iatrogenic	Canalicular laceration, ductal injury in conjunction with naso-orbital-ethmoid fractures
Mechanical	Internal	Dacryolith, migrated or retained medical device
	External	Kissing puncta, conjunctivochalasis

2.4.3 Dysfunction in active lacrimal drainage

In the absence of lacrimation and lacrimal drainage obstruction, epiphora is assumed to be the result of reduced function in active tear drainage, for instance, reduced efficiency of the mechanical tear pump due to age-related changes such as eyelid laxity, or defective

innervation of the periocular muscles caused by facial nerve palsy, tumor or trauma. It is not known whether the vascular plexus surrounding the lacrimal sac and nasolacrimal duct or the absorption of tears also plays a part.

Epiphora in this clinical setting is often referred to as “functional epiphora” or “functional block”, however, there is no consensus regarding the definition of these terms. The description used in most studies is symptomatic epiphora with a patent lacrimal system at syringing and the exclusion of lacrimation.[47-52] However, the accepted degree of resistance to irrigation varies, as does the use of other investigative methods, such as the fluorescein dye disappearance test, dacryocystography and dacryoscintigraphy. Some authors argue that the term functional epiphora should be avoided due to the difficulty in differentiating between partial stenosis and drainage dysfunction without stenosis.[53]

In conclusion, as the mechanism of active tear drainage has not yet been completely elucidated, the causes of its dysfunction are also unknown. Furthermore, due to variations in definitions and the probable inclusion of partial stenosis in some published studies, it is very difficult to evaluate the effectiveness of proposed treatments such as eyelid-tightening procedures.

3 LACRIMAL SURGERY

With the exception of botulinum toxin injections into the lacrimal gland, available treatment options for epiphora are all surgical. Unless a completely stenotic canaliculi necessitates the placement of a Jones tube, the main surgical techniques for the treatment of ALDO in Sweden are DCR and canaliculodacryocystoplasty (CDCP). Several factors need to be taken into account when choosing the most appropriate, for example, patient preference, expected success rate depending on the location of stenosis, the availability of the procedure, and the patient's general medical status.

3.1 DACRYOCYSTORHINOSTOMY

Connecting the lacrimal sac to the nasal cavity, thereby bypassing an obstructed nasolacrimal duct, is one of the main surgical strategies used in lacrimal surgery. The basic concept of the procedure has changed very little since its introduction a century ago. An ostium is created by removing the lacrimal bone and part of the frontal process of the maxilla, the nasal mucosa is incised and the lacrimal sac opened creating an anastomosis.

There are variations in the preferred route, the instruments used, and whether mucosal flaps are created, i.e. whether the osteotomy is healed by primary or secondary intention. The anastomosis can be created using the external or the endonasal approach. The external approach has long been considered the gold standard, as the outcome has been more favorable for many years, with reported anatomical success rates between 90% and 98%.[54-58] The success rate reported with the endonasal approach in the late 1900s was between 56% and 70%.[59-61] However, with improved surgical techniques, it has since increased to 89-95%.[20, 22, 55, 62, 63]

As the success rates are comparable, other factors become important when choosing between the external and endonasal approach. The endonasal approach has several advantages, including no visible scar, less swelling and slightly shorter recovery time. An external DCR, on the other hand, can be performed regardless of the size of the nasal cavity or the presence of septum deviation, and allows inspection of the lacrimal sac before the creation of the osteotomy if desired. The choice of approach is probably often based on the preference or competence of the surgeon, local tradition and patient preference. The most common reason for surgical failure is cicatricial contraction at the osteotomy site.[64] Ali et al. concluded that the most important factors for achieving a stable size of the osteotomy are adequate bone removal exposing the entire lacrimal sac and complete marsupialization of the sac with mucosa apposition to facilitate primary intention healing without granuloma formation.[65]

A question often discussed in both external and endonasal DCR is the necessity of inserting a silicone stent following uncomplicated DCR without canalicular stenosis. Routine intubation is very common (Figure 4), and it was previously claimed that intubation would prevent fibrous closure and contracture of the anastomosis.[66] However, the way in which a 0.8 mm silicone stent would prevent the contraction of an anastomosis several mm in diameter has been questioned.[67, 68] It was instead argued that it would contribute to surgical failure, as it is known that the stent may induce the formation of pyogenic granulomas.[69] If a peritubular granuloma is found, stent removal and treatment with steroids are recommended.[70] In

addition, inserting a silicone stent increases the cost of treatment and the risk of complications such as punctal damage and stent prolapse.[68, 69, 71, 72]

Several randomized studies of DCR with and without intubation have been performed, with varying outcome.[68, 72-77] As the difference in success rate between DCR with and without intubation is small, some of these studies have been criticized for being underpowered.[78] Three meta-analyses have been performed, with inconclusive results. In one of these, the results of five randomized trials were pooled and no significant difference was found between the groups, as the difference in success rate was only 1.2%.[79] In another study, the results of 12 randomized controlled trials were analyzed, and it was concluded that intubation with external DCR provided a benefit, while endonasal DCR did not.[80] However, this study was criticized for including cases in which mitomycin C was used intraoperatively.[71] In the most recent meta-analysis, 14 studies were analyzed including 1311 DCR cases. The authors were able to show a significant 5% benefit overall with an 8% benefit of intubation in external DCR, but failed to show any statistically significant difference with and without intubation in endonasal DCR due to few cases in this group.[71]

As a result of the disagreement regarding the mechanism of the supposed positive contribution of the silicone stent, the duration that the stent is left in place is not based on firm evidence or logical reasoning, but rather on local tradition, convenience and guesswork. In the studies mentioned above, the duration of stenting varied from four weeks to four months.

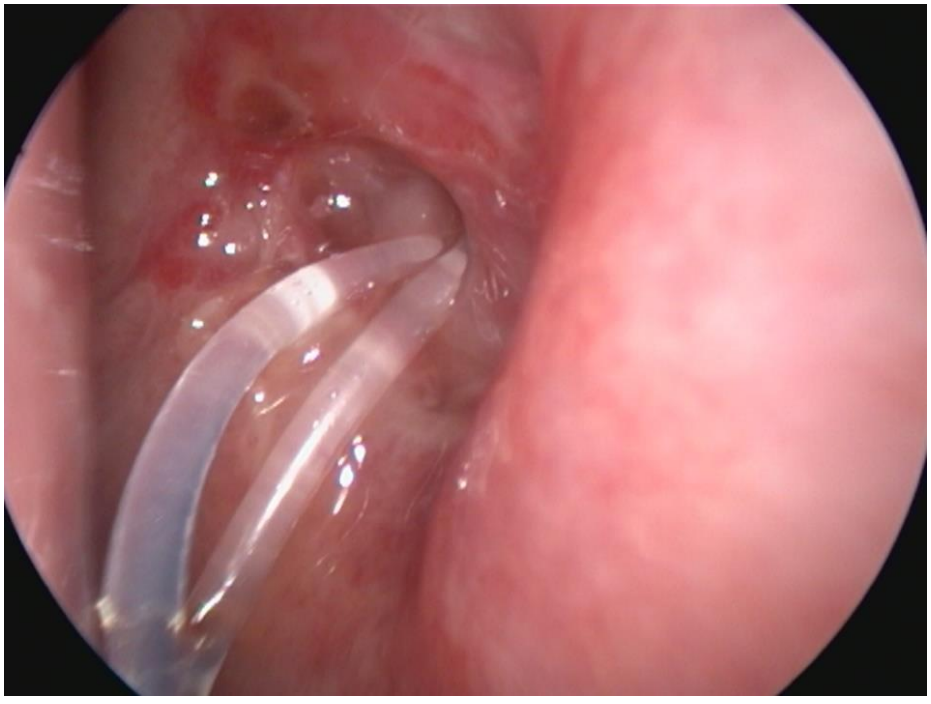

Figure 4: Osteotomy site one week after external DCR surgery with silicone stent in situ. *Photo: Elin Bohman*

According to a theory proposed by Rose, the greatest benefit of a stent, i.e. preventing cross-adhesion and the build-up of exuded fibrin in the canaliculi due to the abraded epithelium, is obtained in the first few days, up to a week.[67] If kept in place longer, the stent may induce a foreign-body reaction triggering granuloma formation and adhesions, thus contributing to failure. Jo et al. reported that pyogenic granulomas were observed after a mean of 46 days (±15 days) post-surgery, which is a common minimum duration of intubation in published studies.[64] The variation in stenting duration could be a possible explanation of the inconsistency of results between studies reporting success rates with and without stenting.

Only one study has been carried out to investigate whether the length of intubation affects the outcome, and this failed to show any significant difference.[81] However, this study suffered from the same problem as the studies mentioned above, of being underpowered. Significant results cannot be expected with only 19/63/46 cases in early/routine/late removal groups when the difference in success rates is only a few percent units. Furthermore, the definition of early removal was before eight weeks, which is decidedly longer than necessary, according to Rose's theory.

3.2 CANALICULODACRYOCYSTOPLASTY

Several procedures, including CDCP, have been developed as simpler, quicker and cheaper alternatives to DCR. Intubation with silicone tubes without simultaneous DCR was first reported by Keith in 1968, and has since become standard practice for congenital lacrimal stenosis not responding to simple probing (Figure 5).[82, 83] The reported success rates in adults vary with the degree and extent of stenosis and follow-up time. Success rates of 83%-88% have been reported for punctal/canalicular stenosis, but when obstruction is confined to the canaliculi, the success rate falls to 65%-76%.[84-88] Studies on partial NLDO (i.e. incomplete obstructions) show good short-term results (6-8 months) with success rates of 75-76%.[89, 90] However, in studies with longer follow-up times (18-29 months), only 47-60% of patients were reported to be symptom-free.[91, 92] Only three studies have specifically investigated the effects of CDCP for the treatment of complete NLDO. In one of them, the authors reported a 52.4% success rate at 12 months in cases with previous dacryocystitis, and 82.9% in cases without previous infection.[93] However, 10% of the patients were excluded for various reasons, and the drop-out rate was almost 25%, leaving only 21 patients in the first group and 35 in the second, making the results less reliable. Inatani et al. reported a 68% success rate in DCG-confirmed complete NLDO, but the follow-up period was only 8 months.[87] The third study included a long-term follow-up (54 months) and reported a success rate of only 22%.[94]

In addition to the above-mentioned studies, there are several others in which the authors did not specify the proportions of partial and complete NLDO, which makes it difficult to evaluate the results.[85, 95-97] In a large study including 994 cases, the only significant positive outcome predictor of CDCP was easy passage of fluid at preoperative syringing.[98]

A number of complications have been reported following CDCP and its variants. Retained stenting material is the most well-known long-term complication.[99] Other common complications are granuloma formation, transient epistaxis, and premature loss of stent and slit punctum.[87, 90, 95, 100, 101]

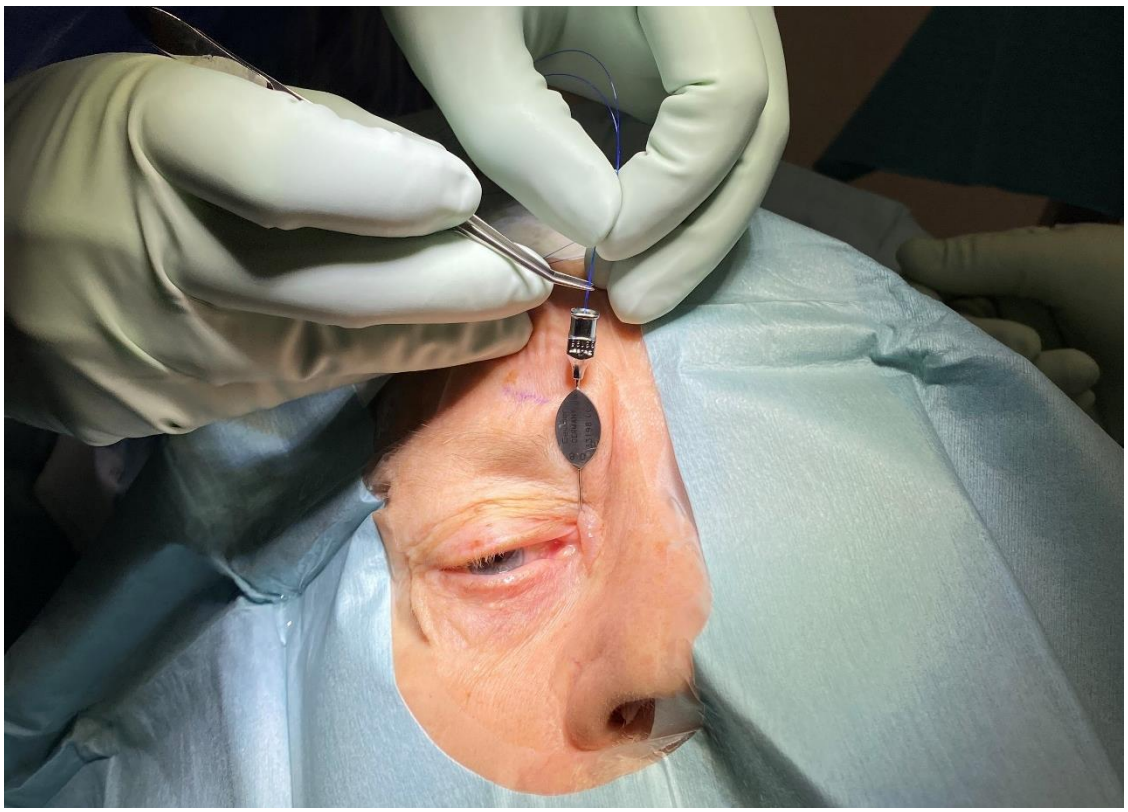

Figure 5: During CDCP the lacrimal drainage system is probed and the obstruction/obstructions bypassed taking care not to create a false passage. The silicone stent is then introduced either by the use of a suture sling, or by a metal guide pre-attached to the end of the stent ("pulled methods"). "Pushed" variants of silicone stents have also been described, where the metal guide is inside the stent during introduction, and then removed. Silicone stents used in both pulled and pushed methods may be either bicanalicular or monocanalicular (secured with a plug at the puncta). Photo: Caroline Sellström

Infections causing canaliculitis, dacryocystitis and keratitis have also been described.[87, 100, 102] A high rate of complications requiring medical evaluation and treatment will reduce the medical and economic advantages of CDCP methods over DCR.

One question which, to the best of the author's knowledge, has not been the subject of any published study is whether the duration of intubation affects the outcome. The duration of stenting in the articles surveyed varied from 6 weeks to 10-11 months; about 3 months being the most common.[84, 86, 87, 103] The aim of stenting is to keep the lumen open during epithelial healing and scar maturation, but the time to completed collagen remodeling depends on a number of factors including the degree of inflammation.[104] The length of this healing period in the lacrimal drainage system is not known. In the case of the soft tissues around dental implants, for example, the epithelium takes 7-14 days to heal, while remaining tissues need 6-8 weeks for scar maturation to be complete.[105] However, the healing period in such cases applies to a surgically created wound, while most cases of ALDO are the consequence of an inflammatory process that may still be ongoing. It thus appears to be logical to keep the silicone stent in place for at least 8 weeks, but it is unknown whether a longer duration improves the success rate.

Variations of CDCP, for example CDCP combined with adjunctive procedures or with topical medication have been described in the literature, but these are used very infrequently in Sweden. Trials have been carried out with single- and double-stent intubation, but no significant difference in outcome was found.[92] The obstruction has also been removed using a trephine burr, but the outcome was no better than with standard CDCP.[106] Balloon dacryocystoplasty, alone or combined with trepanation, has shown good short-term outcome, but the success rate decreased at longer follow-up times.[23, 103, 107] Studies including the use of mitomycin-C have not shown increased success rates, nor has the addition of corticosteroids.[90, 108, 109] In a single study, the use of rebamipide, a topical medication used in dry-eye disease to promote epithelium healing, increased the success rate of CDCP significantly, but this result must be verified in a randomized trial.[110]

In conclusion, there is currently little evidence supporting the use of CDCP to treat complete or near-complete obstructions, and further studies are required into the long-term outcome. If CDCP proves to be an effective treatment option, the optimal duration of silicone stenting must be determined. No adjunctive procedure or medication have yet been proven significantly better than CDCP alone.

3.3 MEASUREMENTS OF FUNCTIONAL SUCCESS IN LACRIMAL SURGERY

Improvement in patient-reported quality of life is being increasingly recognized as an equitable measure of success in health care. Functional success in lacrimal surgery is generally reported as being lower than anatomical success, probably due to factors involved in the mechanisms of active tear drainage that we are not yet able to evaluate and treat. Several different scales have been used to evaluate the functional outcome of surgery and the impact of epiphora on daily life. A questionnaire used in several studies is the Glasgow Benefit Inventory.[111, 112] This is a generic patient-reported outcome measure (PROM) designed to measure the benefit of a surgical procedure. When applied to lacrimal surgery, DCR has been found to have a positive impact on patients' health status, with scores of between +15 and +40 (scale -100 to 100, where zero indicates no benefit), while the score for CDCP has been reported to be +17.[113-118] As this questionnaire was constructed for different medical conditions, it will inevitably lack precision when used to investigate the specific problems associated with epiphora. The Lac-Q questionnaire is a more epiphora-specific PROM.[119] Using this questionnaire, DCR has been found to significantly reduce both lacrimal symptoms and social impact.[120, 121] Other PROMs have also been developed to measure the impact of epiphora, for example, the Nasolacrimal Duct Obstruction Symptom Score, and the National Eye Institute Visual Function Questionnaire, but these are not widely used.[122, 123]

Only one study has been carried out in which the subjective visual impairment caused by epiphora was compared with that resulting from another disease affecting vision. Kafil-Hussain and Khooshebah used the visual function index in a small study performed in 2005, and found that the visual disability resulting from epiphora was comparable to that in patients referred for second-eye cataract surgery.[24]

4 RESEARCH AIMS, STUDY DESIGN AND ETHICS

4.1 RESEARCH AIMS AND STUDY DESIGN

The overall aim of the work presented in this thesis was to study different aspects of epiphora and treatments of lacrimal obstructions in order to aid health care professionals in deciding on appropriate interventions and to be able to inform patients adequately.

The specific aims of the study described in Paper I were to evaluate the subjective visual disability experienced by patients with epiphora due to lacrimal drainage obstruction in relation to another ophthalmic disease (cataract), and to validate the use of a self-assessment questionnaire measuring limitations on daily life activities due to visual disability (the Catquest-9SF) on epiphora patients. A survey of patients with confirmed ALDO was carried out using the Catquest-9SF and the results were compared with data from the Swedish National Cataract Register.

The purpose of the study described in Paper II was to survey current practices in the treatment of lacrimal drainage obstructions in the Nordic countries (Finland, Norway, Denmark, Island and Sweden), and to identify challenges in providing a good lacrimal health care. An online survey was carried out using a 16-item questionnaire regarding the management of ALDO among the ophthalmological clinics in the Nordic countries that offer lacrimal surgery (Paper II).

The third study was a cohort study of adult patients with complete ALDO, treated with CDCP and performed with the aim to investigate the long-term outcome of CDCP in relation to the anatomical location of the lacrimal obstruction.

The following study (Paper IV) was a non-comparative cohort study carried out to evaluate the long-term outcome of DCR with one-week silicone stent intubation

The final study was an experimental study, in which stenotic and healthy lacrimal drainage systems were examined with ultra-high-frequency (UHF) ultrasound, and motion tracking of the lacrimal sac wall during blinking was performed in order to elucidate the mechanisms governing active lacrimal drainage (Paper V).

4.2 ETHICS

Approval for the first study was obtained from the Ethics Committee at Karolinska Institutet, Stockholm Sweden. All epiphora patients were fully informed about the study, including the fact that participation was voluntary. They gave their written informed consent by signing the questionnaire.

The Ethics Committee at Karolinska Institutet, Stockholm, Sweden, concluded that no ethical approval was needed for the second study as no item in the questionnaire concerned individual patients. In an advisory statement, the Committee specified that they had no ethical objections to the study. An application for ethical approval was also submitted regarding the follow-up of patients with lacrimal drainage obstructions treated with lacrimal surgery (DCR

or CDCP) (Papers III and IV). The Committee concluded that this was a question of quality assurance, and therefore exempt from requirement of ethical approval.

All patients participating in the final study (Paper V) received information about the study including the voluntary nature of participation, and gave their written consent. The Ethics committee at Lund University approved of the original application (concerning eyelid examination), as well as an additional application including the experimental protocol for the examination of the lacrimal drainage system.

All research was conducted in accordance with the Declaration of Helsinki.

5 SUBJECTS AND METHODOLOGICAL CONSIDERATIONS

5.1 SUBJECTS

5.1.1 Patients and controls in Study I

Consecutive patients referred to the Oculoplastic and Orbital services at St. Erik Eye Hospital due to epiphora complaints and who at examination were confirmed to have a lacrimal drainage obstruction, were asked to participate. Exclusion criteria were age below 18, inability to give informed consent (mental disability/dementia/language problems), lacrimation (for example eyelid malposition or trichiasis), congenital nasolacrimal duct obstructions or secondary lacrimal obstruction due to mucous membrane disease (sarcoidosis, granulomatous polyangiitis), tumor, trauma or previous chemotherapy.

5.1.2 Centers surveyed in Study II

All clinics affiliated to the National Health Services and all private ophthalmological centers that offered any form of lacrimal surgery were identified via the Nordic Society of Oculoplastic and Reconstructive Surgery and official lists of ophthalmological clinics in each country. In total, 79 clinics in Finland, Denmark, Norway, Island and Sweden were identified and invited to take part in the study.

5.1.3 Patients in Study III

Adult patients (>18 years) who had received treatment with CDCP for a complete, non-infected ALDO at St. Erik Eye Hospital between May 2011 and August 2012 were invited to participate. There is no overlap between this study group and the patients participating in Study I. If the patient was treated bilaterally, they were included as two separate cases. Exclusion criteria consisted of factors that could contribute to a lower success rate: eyelid malposition, facial nerve palsy, tumor in the medial canthal/lacrimal drainage area, mucous membrane disease, previous lacrimal surgery, chronic dacryocystitis, traumatic stenosis or nasal fracture affecting the lacrimal duct. Patients unable to give informed consent were also excluded.

5.1.4 Patients in Study IV

Adult patients (>18 years) with NLDO treated with external DCR with one-week silicone tube intubation at St. Erik Eye Hospital between May 2011 and September 2012 were asked to participate in the study. The only exclusion criterion was inability to give informed consent. The presence of canalicular stenosis, fibrosis of the lacrimal sac or any intra-operative problems with mucosal flaps would prompt the surgeon to decide on a longer intubation period, and consequently all surgeries included in the study were uncomplicated. However, the etiology of the NLDO, or a history of previous or present current infection, did

not motivate an extended period of intubation, and patients with secondary NLDO and those with dacryocystitis were therefore included.

5.1.5 Patients in Study V

Fourteen adult patients with uni- or bilateral epiphora referred to the Department of Ophthalmology, Skåne University Hospital in Lund, were invited to participate. One patient declined to participate, and only the affected side was examined in four patients, resulting in 22 investigated lacrimal drainage systems. The result of the fluorescein dye disappearance test indicated pathology in 11 lacrimal drainage systems, and stenosis was confirmed by syringing in 10 cases.

5.2 METHODOLOGICAL CONSIDERATIONS

5.2.1 Effects on quality of life in epiphora and cataract patients

Cataract is a common, well-known eye disease affecting visual acuity, and patients awaiting cataract surgery therefore constitute a relevant reference group for comparison of visual disability with epiphora patients in Study I. Catquest-9SF is a short form of the original Catquest questionnaire developed to measure cataract patients' self-assessed impact on limitations in daily life activities due to visual disability.[124, 125] It is used pre- and postoperatively to evaluate surgical benefit, and the results are collected in the Swedish National Cataract Register. The Catquest-9SF contains two global assessment items and seven disability items (Table 2). There are four response options for each item; the options for the second global item are 'Very satisfied'; 'Fairly satisfied'; 'Fairly dissatisfied'; and 'Very dissatisfied'. For the seven disability items and the first global item the responses are 'No difficulty'; 'Some difficulty'; 'Great difficulty'; and 'Very great difficulty'. All items also include the option 'Cannot decide'. A higher score indicates a higher degree of perceived disability, and a lower score, less disability, for all items. The epiphora patients with confirmed lacrimal drainage obstructions were asked to complete the Catquest-9SF questionnaire (original Swedish version) before and after surgery. The results regarding the degree of satisfaction of epiphora patients with surgery were not analyzed as the aim of this study was to compare the visual disability of cataract and epiphora patients before surgery. An epiphora-specific PROM would have been more suitable to investigate improvement after lacrimal surgery.

Table 2: The items in the Catquest-9SF questionnaire (official British English version)

Global assessment items	
1	Do you find that your sight at present in some way causes you difficulty in your everyday life?
2	Are you satisfied or dissatisfied with your sight at present?
Disability items: Do you have difficulty with the following activities because of your sight?	
3	Reading text in newspapers?
4	Recognizing the faces of people you meet?
5	Seeing the prices of goods when shopping?
6	Seeing to walk on uneven surfaces, e.g. walking in the forest?
7	Seeing to do handicrafts, woodwork etc.?
8	Reading subtitles on TV?
9	Seeing to engage in an activity/hobby that you are interested in?

5.2.2 Survey of the current practice of lacrimal disorders in the Nordic countries

A 16-item questionnaire was created using an online platform (Survey Monkey Inc.). An invitation to participate in the study was sent to the head of the department or the person in charge of lacrimal surgery at the 79 identified ophthalmological clinics in the Nordic countries. The questions concerned the frequency of lacrimal surgical procedures, which specialists performed lacrimal surgery (ENT surgeons or ophthalmologists), referral rates and current management practices for different types of acquired lacrimal obstructions (a complete list is given in Paper II). A follow-up invitation was sent to those clinics not responding six to eight weeks later. The responding clinics were identified by country and whether they were academic, regional or private clinics. The person responding to the

questionnaire was asked to give responses that reflected general practices at the clinic and not personal opinions. No item was mandatory, and the questionnaire was constructed in such a way that the response to a question affected the next presented question. For example, if a center did not perform DCR surgery, all following items concerning DCR surgery were bypassed. Because of this, the number of responses to each item varied.

5.2.3 Long-term outcome of CDCP depending on location of stenosis

For Study III, patients with the highest probability of a favorable outcome were chosen, i.e. patients with no risk factors for restenosis, in order to determine the best possible outcome for each location of stenosis. This was assessed through anamnesis and eye examination at the preoperative visit. The location of the stenosis was determined through both preoperative syringing and intraoperative probing. All examinations and operations were either performed by, or supervised by, a senior oculoplastic surgeon. During surgery, a monocanalicular stent (FCI Monoka, Paris, France) was placed in a standard fashion as no case required bicanalicular intubation (a detailed description of the procedure is given in Paper III). Any complications during the study period were noted. The primary endpoint was defined as the date for reoperation of stenosis or, if the patient declined further surgery, the date of confirmation of restenosis. The reason for defining the endpoint in this way was due to the uncertainty as to when exactly the stenosis reformed. At the end of the follow-up period in June 2018, a questionnaire regarding current epiphoric problems in the operated eye was sent to all patients who had not required additional lacrimal surgery.

5.2.4 Outcome of DCR with one-week silicone stent intubation

When the role of silicone stent intubation in conjunction with DCR is discussed among lacrimal surgeons, these discussions refer to uncomplicated surgeries as there is consensus that intubation is required in cases of canalicular stenosis or a contracted lacrimal sac. Consequently, when investigating the outcome of an intubation period that is shorter than previously described as in Study IV, it was reasonable to select patients undergoing uncomplicated DCR surgery. During surgery, a bicanalicular silicone stent (O'Donoghue DCR set, BVI Visitec, MA, US) was placed as described in Paper IV. It was removed one week postoperatively, at the same time as the removal of skin sutures. Pre- and perioperative findings were noted, and any complications or recurrence of epiphora requiring additional surgery during the 4 year follow-up were recorded. At the end of the follow-up period, a questionnaire was sent asking patients to grade their epiphoric problems in the operated eye as never/seldom or often/constantly.

5.2.5 Investigation of the movements of the lacrimal sac using UHF ultrasound

Ultrasound is a non-invasive imaging modality capable of producing *in vivo* images of tissues under physiological conditions and, with recent developments of UHF ultrasound, it is now suitable for investigation of the lacrimal drainage system and its movements during the blink cycle. In Study V, a Vevo 3100 ultrasound imaging system (FUJIFILM VisualSonica Inc., Toronto, ON, Canada) was used. The system was equipped with three linear array transducers achieving axial resolutions of: 50 µm (MX400 transducer, central frequency 30 MHz,

bandwidth 20-46 MHz), 40 µm (MX550 transducer, central frequency 40 MHz, bandwidth 25-55 MHz) and 30 µm (MX700 transducer, central frequency 50 MHz, bandwidth 29-71 MHz). The transducer giving the best possible image quality was chosen depending on the size of the structure to be examined and its depth below the skin surface.

Prior to investigation with ultrasound, all patients underwent examination of the eye, eyelids and lacrimal drainage system. During ultrasound investigation, the lacrimal drainage system was irrigated with a lipid-containing fluid (Intralipid®, Fresenius Kabi AB, Uppsala, Sweden) to confirm the location of the lacrimal sac and to exclude or confirm the presence of obstruction. This irrigation solution was chosen as lipids enhance ultrasound visualization. The puncta and the canaliculi were scanned, as well as the lacrimal sac including adjacent vessels, specifically the angular vein. Ultrasound gel was used to achieve good acoustic coupling, and the utmost care was taken not to compress the lacrimal drainage system during examination.

No safety assessment was made specifically for this study as the safety of the ultrasound system had been evaluated in a previous study and identical settings were used.[126]

5.3 DATA ANALYSIS AND STATISTICS

Rasch analysis is a mathematical model used in the field of psychological measurements for categorical data such as responses to a questionnaire, and is the statistical method used to analyze the Catquest-9SF responses in the Swedish National Cataract Register.[127] Consequently, it was the statistical method used in Paper I. Rasch analysis may be used to validate a questionnaire for a specific group of patients and to compare answers to the same questionnaire by different groups. In order to validate the questionnaire, the relation between the respondents' ability to carry out the activities and the difficulty of the activities is analyzed. This was done by analyzing the following psychometric properties: rating scale, ability to discriminate different strata of person ability, item fit statistics, targeting precision of the instrument to the studied population and unidimensionality. The response options in the Catquest 9SF were given numerical values of 1-4, where 1 indicates "no difficulties" or "very satisfied" and 4 "very great difficulties" or "very dissatisfied". The option "cannot decide" was assigned the value 0. This provided nine raw scores per patient. It should be noted that in the questionnaire itself the response options are presented in reverse order, with the option for greatest difficulty first. To compare the study group to the reference groups the ordinal raw data were converted to a mean person score per group on a linear Rasch scale (logit) from -5.43 (no activity limitations) to +5.01 (severe activity limitations). Based on clinical experience, it was assumed that a clinically relevant difference in visual disability was equivalent to ±1 logit or more. An equivalence test was performed by calculating the 95% confidence interval for the mean difference in person Rasch score between compared groups. If the confidence interval included zero and the upper and lower limits were within ±1, the groups were concluded to have activity limitations in parity with each other.

The responses to the questionnaire are presented descriptively as absolute numbers and percentages in Paper II. No statistical analysis was performed.

Survival analysis was employed using the Gehan-Wilcoxon test to calculate the survival rate (Paper III). This statistical method was chosen as the time between primary surgery and

reoperation was of interest, and not only the final outcome. Survival time (time-to-event) was defined as time from primary surgery to reoperation. The prevalence of secondary causes of ALDO differs between age groups, and undetected secondary causes may be a confounding factor if unequally distributed. When plotted in a histogram, age was seen to have a non-Gaussian distribution, and was therefore compared between study groups using the Kruskal-Wallis test by ranks. The significance level was set to 5%. The number of complications and the response to the questionnaire regarding epiphoric problems at the end of follow-up are presented descriptively in absolute numbers and, when appropriate, percentages.

A dropout analysis was performed after Paper III had been published comparing cases with and without response to the end-of-follow-up questionnaire with regard to age, gender and location of stenosis. The Mann-Whitney U test was used to compare the age distribution. In addition, the chi-squared test was used to compare the distribution of gender (categorical variable, >5 cases per category) and Fisher's exact test for location of stenosis (categorical variable, <5 cases per category).

The data in Paper IV are presented descriptively in absolute numbers and percentages. No statistical analysis was performed.

The movement of the lateral wall of the lacrimal sac during blinking was quantified using two-dimensional speckle tracking (Paper V). This technique tracks the distance the kernels (i.e. image components) have moved between consecutive frames with a known frame rate, allowing the direction and magnitude of movement to be determined. Speckle tracking was employed at five different locations in the lumen to estimate blood flow. The inner diameter of the vessel was measured and the assumed circular cross-sectional area calculated. Volumetric blood flow was then obtained by multiplying the mean velocity by the estimated cross sectional area of the lumen.

Statistical analysis of the difference in depth below the skin surface was performed using the Mann-Whitney U test. The significance level was set to 5%.

6 RESULTS AND DISCUSSION

6.1 CATQUEST-9SF AND LIMITATIONS ON ACTIVITIES IN DAILY LIFE DUE TO EPIPHORA

In all, 72 patients were included in the first study. Reference groups were made up of patients with complete data from a preoperative Catquest-9SF questionnaire in the Swedish National Cataract Register during the month of March 2013. This provided two reference groups: 2096 patients awaiting first eye cataract surgery, and 1529 patients awaiting second-eye cataract surgery.

The first aim of this study was to validate the use of Catquest-9SF in patients with epiphora and confirmed lacrimal drainage obstructions. When Rasch analysis was employed to test the psychometric qualities of the questionnaire on this group of patients it showed a misfit for item 4 (ability to recognize the faces of people you meet). It is unclear why this showed an item misfit, but patients with epiphora often describe greater difficulties when looking down, due to increased tear meniscus which distorts the visual axis.[24] When meeting people, one usually looks up, through a less irregular part of the tear film, which could explain the misfit. In addition, other factors may contribute to recognizing a person, such as height, gait, or body language, etc., and this may influence the level of perceived difficulties.

After the exclusion of item 4, a new analysis showed that an 8-item version of Catquest-9SF was a valid measure of limitations on activities in daily life due to visual disability in epiphora patients. When using this questionnaire to evaluate epiphora patients one should bear in mind that it only measures one aspect of the difficulties perceived by patients with epiphora, i.e. their visual disability. It does not take into account the need for frequent wiping and resulting sore eyelid skin or the social embarrassment that may be caused by the constant appearance of crying. However, it does allow comparison with disturbances in visual function associated with other ophthalmic diseases.

The second aim was to compare the perceived visual disability measured by the 8-item Catquest-9SF questionnaire with the recorded preoperative response of patients awaiting cataract surgery in the Swedish National Cataract Register during March 2013. Patient characteristics are given in Table 3. Female dominance in the epiphora patient group is in line with several previous studies showing a significantly higher incidence of lacrimal obstructions in women.[17-19, 30] It should also be noted that the epiphora patients in this study were, on average, more than 10 years younger than the patients in the two reference cataract groups. As the normal retirement age in Sweden is 65 years, this means that a majority of the epiphora patients are probably still working, and their difficulties may interfere with their occupation.

The equivalence test showed that the perceived visual disability of epiphora patients was in parity with that of patients awaiting second-eye cataract surgery, but lower than that of patients waiting for first-eye cataract surgery. The only other comparison of subjective visual function between patients with epiphora and patients with cataract to date is that published by Kafil-Hussain and Khooshebah in 2005.[24] The findings of the present study are in agreement

with their results, as they concluded that epiphora patients suffered equal, if not more, limitations on activities in daily life as patients waiting for second-eye cataract surgery.

One limitation of the present study is that comorbidity was not taken into consideration, and given the difference in mean age between the groups, this may have affected the cataract patients to a greater extent, possibly leading to over-estimation of the visual disability caused by cataract alone. Another limitation is that the only common denominator between epiphora and cataract is that it affects visual function, which should also be borne in mind when comparing the groups.

In summary, an 8-item version of the Catquest-9SF questionnaire is a valid tool for measuring limitations on activities in daily life due to visual disability in patients with epiphora. The visual disability experienced by epiphora patients is in parity with that of patients awaiting cataract surgery in their second eye.

Table 3: Characteristics of the epiphora patients and cataract control groups compared in Paper I

Group	Gender (% female)	Mean age (range)
Epiphora patients, n=72	72%	59.5 years (19-88)
First eye cataract surgery patients, n=2096	60%	73.6 years (20-98)
Second eye cataract surgery patients, n=1529	62%	74.6 years (41-98)

6.2 CURRENT PRACTICES IN THE MANAGEMENT OF LACRIMAL DISORDERS IN THE NORDIC COUNTRIES

The purpose of the study presented in Paper II was to survey current management of ALDO and functional epiphora in the Nordic countries (Finland, Denmark, Norway, Island and Sweden), to serve as a basis for the discussion of optimal management. Fifty-one out of 79 clinics responded to the questionnaire, giving a response rate of 65%. Within the Nordic countries, CDCP is performed at the majority of clinics, whereas DCR surgery is more centralized, and half of the clinics refer patients to other centers for this procedure. Several respondents expressed the opinion that there was a lack of opportunity for surgical training in DCR surgery. These two factors may explain why CDCP is considered as an option for the primary procedure not only in cases of obstructions proximal to the lacrimal sac, but in 51% of the clinics also for non-infected NLDO. At some clinics, CDCP was still an option in cases

of current chronic or previous acute dacryocystitis, previous nasal trauma or recurrent obstructions. This choice of treatment may be questionable, as there are few studies reporting the success of CDCP for complete ALDO, as outlined in Chapter 3.

An area in which there seems to be a lack of consensus is the duration the silicone stent should be left in place following CDCP. Ophthalmologists in Denmark and Norway* choose a shorter intubation period, removing the stent after three months, while the majority of clinics in Sweden and Finland wait six months before removing the stent. It is unclear whether this difference in stenting duration affects the outcome as the duration of stenting in CDCP has not been the subject of any published studies.

Generally, a conservative approach to surgical treatment of functional epiphora is employed in the Nordic countries. Only half the clinics were likely to offer eyelid-tightening surgery in order to improve the effect of the lacrimal pump, and only 16 clinics offered lacrimal surgery: one offering DCR and 15 CDCP. As the success rate of DCR surgery for this indication is considerably *lower* than when a lacrimal obstruction is present, with reported rates of only 50%-55%, it is reasonable to reserve DCR for exceptional cases.[128, 129] However, several studies have reported surprisingly high success rates of CDCP, 69%-77%, when treating functional epiphora.[47, 52, 130] This is considerably higher than the long-term success rates reported when partial ALDO is treated with CDCP (47%-60%).[91, 92] However, in all the above studies, patients were asked to grade their current epiphora problems in relation to their preoperative problems, and the results may have been affected by recall bias. Eyelid-tightening surgery is effective in 63%-87% of cases, and may be a reasonable approach in cases of severe symptoms in conjunction with pronounced lower eyelid laxity.[48-50, 131]

The respondents were asked to answer the questionnaire based on the actual policy at their clinic, and not to give their personal preferences or opinions. However, there is always the risk that responses will reflect personal opinions to a certain degree. Another limitation of the present study is that the questionnaire was not validated before use. It is also possible that respondents unhappy with the state of the lacrimal service at their clinic were more likely to respond.

Is summary, there appears to be frustration among physicians providing lacrimal services in the Nordic countries due to the fact that needs exceed resources. It is therefore important to establish a consensus regarding indications for surgery, so that each patients receives the optimal treatment. There is also a need to address training and the transfer of skills to ensure competence within the field of lacrimal surgery in the future. Above all, the long-term outcome of CDCP when treating complete ALDO requires clarification if this practice is to continue.

6.3 LONG-TERM OUTCOME OF CDCP

As the study described above showed that CDCP was being used to treat complete ALDO in the Nordic countries despite any firm evidence of its efficacy, the next study was carried out to investigate the long-term outcome of CDCP in these cases. It was hypothesized that CDCP would have a more favorable outcome when treating canalicular stenosis than when treating NLDO.

A total of 87 cases of complete ALDO treated with CDCP in 72 patients without any known risk factor for restenosis were included in this study. One patient died from unrelated causes two weeks after the bilateral operation, and was therefore excluded, giving a final number of 85 cases in 71 patients. At end of the 76-month follow-up, reformation of stenosis was confirmed in 33 cases, and these patients had either received, or been offered, additional lacrimal surgery, giving an overall reoperation rate of 39%.

In this study, 57 cases were classified via lacrimal irrigation as canalicular stenosis and 28 as NLDO at the preoperative visit and when survival analysis was employed. No statistically significant differences were found between these two groups (p=0.49).

During CDCP, 25 of the 57 presumed cases of canalicular stenosis were found to have an additional stenosis below the lacrimal sac. The three groups (canalicular stenosis, NLDO, and combined canalicular stenosis and NLDO) were compared using multivariate survival analysis, and the difference between them was found not to be statistically significant (p=0.09). However, if the groups had been larger, it is not unreasonable to speculate that significant differences may have been found. In accordance with the above hypothesis, the group with stenosis only in the canaliculi was compared with the two other groups combined (Figure 6). This analysis showed a significantly higher survival rate when stenosis was confined to the canaliculi (p=0.03).

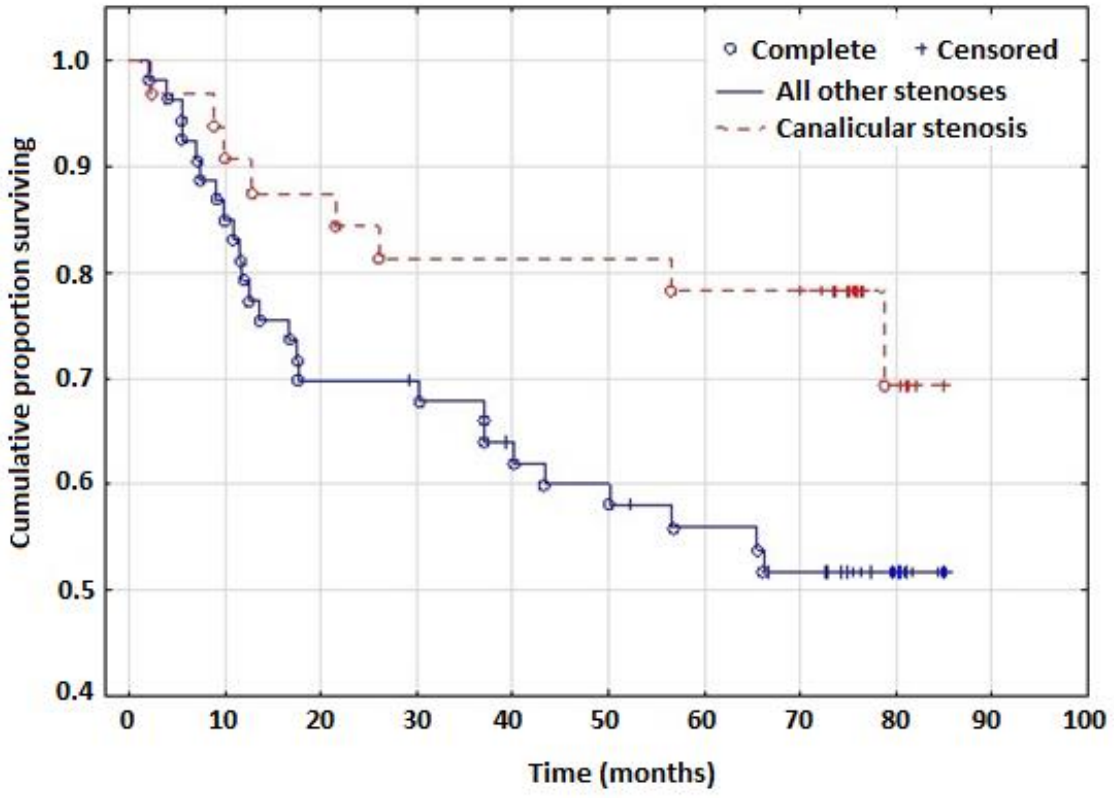

Figure 6: Comparison between cases of stenosis confined to the canaliculi and all other locations of stenoses (NLDO or combined canalicular stenosis and NLDO) (p=0.03).

As can be seen in Figure 6, the majority of patients receiving additional surgery did so within the first two years after the initial procedure, although a not insignificant fraction of cases underwent surgery later. The time between recurrence of epiphora and treatment of confirmed restenosis may be prolonged due to several factors, including patient delay and waiting times for a clinic appointment and operation. Based on the above findings, one may suspect that most stenoses reform within the first years after CDCP.

The most common complication following CDCP in this study was premature loss of the silicone stent, accounting for 10 of 19 negative events. This is in line with the frequency of complications described in the literature.[87, 94] In seven cases, the anchoring plug of the monocanalicular stent touched the surface of the eye causing irritation, and in one case it caused corneal abrasion. As no bicanalicular stents were placed, no cases of slit puncta were seen. In addition, there was one case of pyogenic granuloma and one case of acute dacryocystitis seven years after CDCP prompting systemic antibiotic treatment and subsequent DCR. The latter is obviously a consequence of reformed stenosis, and not a complication resulting from CDCP per se, but was nonetheless noted as a negative event.

Not everyone contacts their doctor when symptoms recur, and there is a difference between not having received additional surgery and being free from symptoms. For this reason, a questionnaire was sent out to the patients with the 52 cases that had not been reoperated at the end of the follow-up period. Responses were received for 37 cases (response rate 71%). Table 4 summarizes the characteristics of the cases for which responses were received and those who did not respond. No significant difference was found between the groups regarding the distribution of sex ($p=0.56$, chi-squared test), age ($p=0.94$, Fisher's exact test) or location of stenoses ($p=0.86$, Mann-Whitney U test). Among the patients who responded, epiphora was reported often/constantly in 11 cases (30%) and never/seldom in 26 cases (70%).

One limitation of this study is that the non-reoperated cases had not been reexamined to confirm lacrimal drainage patency. The true survival rate of CDCP may thus be lower than that found here, based on the 30% of cases who had recurrent problems with epiphora. Another limitation is that the location of the reformed stenosis was not noted and there is a possibility of iatrogenic stenosis at another location, rather than true restenosis. On the other hand, this is more of an academic question, as it would not affect the subsequent treatment.

Bearing in mind that survival rate was defined as time to additional surgery and not equal to success rate, it is possible to compare the present findings with results in the literature. When comparing the findings regarding isolated canalicular stenosis using the corresponding time in Figure 6 these are in line with the 76% success rate at 15 months presented by Fulcher et al., and the 65% success rate at 72 months reported by Connell et al.[84, 85] Regarding treatment of complete NLDO, Inatani et al. reported a 68% success rate after 8 months,[87] in good agreement with the present study. In contrast, Angrist and Dortzbach reported only 22% successful outcomes after 54 months, [94] which is considerably worse than other studies. This may have been an effect of the small sample size, 8 patients, with complete NLDO in their study.

Table 4: Characteristics of the 52 cases receiving the end-of-follow-up questionnaire

	Number of cases	Mean age (y)	Sex (% female)	Intra-operative location of stenosis
Cases with response from the patient	37	61	62%	16 canalicular 13 NLDO 8 combined
Cases without response from the patient	15	61	53%	7 canalicular 4 NLDO 4 combined

In conclusion, the hypothesis that CDCP is more successful in treating isolated canalicular stenosis than stenosis at any other location was confirmed. Despite this, approximately 30% of patients with canalicular stenosis required additional surgery within 72 months. In patients with NLDO or multiple stenosis this fraction is almost 50%. This should be compared with the 89-98% success rate after DCR reported in numerous studies, regardless of the location of stenosis.[20, 22, 54-58, 62, 63] When discussing treatment options with a patient, the choice between DCR and CDCP is not simple as both patient-specific considerations and health care economic aspects must be taken into account. DCR is a more extensive procedure, requiring greater resources, however, this may be offset by the reduction in visits due to complications or the recurrence of epiphora following CDCP and the reduced need for additional procedures.

6.4 DURATION OF STENTING AFTER DCR

For the past 20 years, it has been standard practice at St. Erik Eye Hospital following uncomplicated DCR surgery to keep the silicone stent in place for only one week. This is cost-effective for the care provider and convenient for the patient as there is no need for a routine second visit. This is a shorter duration of intubation than reported previously, so a study was carried out to investigate the long-term success rate after DCR with one-week intubation (Paper IV).

In this study, 70 cases ALDO in 67 patients treated with DCR and one-week intubation were followed. The age (median 57 years, range 24-88 years) and gender distribution (76% female) were in line with previously published studies.[20-22] In 38 of the 70 cases, there was either a history of previous acute dacryocystitis or intraoperative signs of chronic infection. In two cases a dacryolith was found in the lacrimal sac intraoperatively, and in one case a

retained silicone stent from a previous CDCP. Only one complication was encountered, a case of postoperative epistaxis and notably, no stent-related problems were reported.

During follow-up, one patient (one case) needed additional surgery as examination prompted by recurring epiphora revealed a large middle turbinate partly covering the osteotomy. In addition, three patients (three cases) died from unrelated causes, and consequently the end-of-follow-up questionnaire was sent to the remaining 63 patients (66 cases). The response rate was 88% and showed that a very high proportion of patients (54 of 58, 93%) experienced epiphora never or seldom.

The four patients (four cases) who reported epiphora occurring often or constantly were offered a follow-up visit and three accepted. In two cases, the osteotomy had healed well and the canaliculi were patent. The last case showed signs of general inflammation of the nasal mucosa with multiple adherences, and the patient was referred to the ENT department due to suspected systemic mucous membrane disease.

The functional or anatomical success rate was 97%, which is comparable with the highest success rates published.[56, 57] However, the findings of this study only show that a high success rate is possible with a very short intubation period. The conclusions that can be drawn from this finding are limited by the non-comparative nature of the study. Another limitation is that not all patients were examined to confirm anatomical patency at the end of follow-up, as an obstructed lacrimal drainage system may not lead to symptomatic epiphora.

One of the problems regarding the role of silicone stenting in conjunction with DCR surgery is that it is not known exactly what, if any, possible positive effects the stent may have. If a stent is not needed, omitting it would reduce the cost of the procedure, which may be an important factor in some countries.[68] On the other hand, if the theory proposed by Rose is correct, and the silicone stent provides drainage preventing the build-up of fibrin and preventing cross adhesions in the canaliculi, this could motivate the use of stents.[67] A one-week intubation period appears to be sufficient, and in addition, one week is a sufficiently short time not to trigger granuloma formation, and the risk of other stent-related problems would thus be very low.

There may well be an optimal duration of intubation, providing possible positive effects, while minimizing complications. However, a randomized trial that is adequately powered would be needed to determine this duration. To obtain a rough estimate of the number of patients needed, a power calculation was performed using the success rate in the present study (97%) and that for uncomplicated non-intubated external DCRs reported by Saiju et al. (87% success rate, 56 patients)[68] The difference in success rates is 10% and, to ensure that a 10% difference could be detected at a significance level of 5% with a certainty of 80%, a minimum number of 114 cases would be needed in each arm of the study.

In conclusion, a very high long-term success rate was observed with only one-week silicone stenting. Nevertheless, further studies are required to determine whether or not it is necessary or advantageous to insert silicone stents in DCR surgery.

6.5 IMAGING OF THE UPPER LACRIMAL DRAINAGE SYSTEM WITH UHF ULTRASOUND

The final study was carried out to investigate the upper lacrimal drainage system with UHF ultrasound and to demonstrate the *in vivo* movements of the lacrimal sac during blinking.

The lacrimal sac has sometimes been described as a distended cavity.[132, 133] However, this may be the result of preparation of the specimen for histological examination. The study presented in Paper V, which was carried out *in vivo* and under physiological conditions, demonstrated that the normal lacrimal sac lumen is slit shaped, which is in line with the findings of Paulsen et al. and Ayub et al.[3, 10] The wall of the lacrimal sac is known to be highly elastic, from clinical experience of mucocele formation, findings of elastic fibers in the lacrimal sac wall, and from direct visualization via lacrimal endoscopy.[10, 11, 134] This fact was readily demonstrated in the present study when the lacrimal drainage system was irrigated during examination.

This is the first time the puncta and proximal part of the canaliculi have been visualized under physiological conditions, with the eyelids against the globe (Figure 7). In previous ultrasound investigations, only lower frequencies were used, and the canaliculi were below the resolution limit.[135-138] The possibility of visualizing this structure may aid the clinician in evaluating subtle puncta malposition, or determining whether canalicular tissue is present despite puncta agenesis.

During the examination of first patient, a discrepancy was observed between the images of the lacrimal sac and the images presented in two previously published papers.[139, 140] The position of the lacrimal sac was confirmed in the present study by irrigation of the lacrimal drainage system with a clearly visible lipid-containing solution, and was found to be at a median depth of 3.6 mm below the skin surface. This corresponds well with findings in older investigations where ultrasound was performed with lower frequency and resolution.[136, 137] After analyzing the images in the papers published to obtain the dimensions and depth below the skin surface of the structures, we were able to reproduce images of a structure with similar characteristics. This structure was not filled with lipid-containing solution when the lacrimal drainage system was irrigated, and it was located at a median depth of 1.6 mm below skin surface, i.e., significantly more superficial than the lacrimal sac ($p<0.0001$). Using motion tracking, the fluid flow within the structure was estimated to 2.1 ml/min, which is comparable to the blood flow in veins of similar dimensions.[141] The flow of tears in the lacrimal sac was too low to be measured with motion tracking in the present study, however, normal tear drainage has been reported to be 0.05 ml/min using the saline drop test.[142] It was therefore concluded that the angular vein had probably been confused with the lacrimal sac in the studies.

Confusion regarding the nature of examined structures highlights one of the limitations of ultrasound as an imaging modality; i.e., that it is highly user-dependent and experience is needed to correctly identify structures. The findings of the present study may be used in future ultrasound investigations of the lacrimal drainage system to aid localization of the lacrimal sac.

The movement of the lateral lacrimal sac wall during a blink cycle was demonstrated using motion tracking. In contrast to previous theories suggesting that the movement of the lacrimal sac wall is in the medial-lateral direction, only minimal motion was seen in this direction, while greater movement was seen in the anterior-posterior direction. This finding may lend support to the "wrung out" theory of lacrimal drainage, although three-dimensional motion analysis will be needed to completely clarify the dynamics of the lacrimal sac.

Figure 7: Imaging of the upper lacrimal drainage system with UHF ultrasound. On screen, the upper eyelid (to the right) and lower eyelid at the level of the puncta can be seen. Photo: Annika Söderpalm

The lateral lacrimal sac wall has been seen to move in the medial-lateral direction in endoscopic video recordings after DCR.[9, 143] However, removing the bone in the lacrimal sac fossa, possibly damaging the medial canthal tendon, and marsupializing the sac onto the lateral nasal wall, may alter the dynamics of the sac.

One limitation when imaging the lacrimal drainage system with ultrasound is that only the upper system can be visualized, as ultrasound is no longer a feasible imaging modality when the lacrimal duct enters the bony lacrimal canal.

In summary, it is possible to visualize the upper lacrimal drainage system *in vivo* and under physiological conditions using UHF ultrasound. However, care must be taken to identify the anatomical structures correctly. The greatest movement of the lateral lacrimal sac wall during a blink cycle was seen in the anterior-posterior direction. This finding suggests that current theories regarding the lacrimal pump may have to be re-evaluated.

7 SUMMARY AND FUTURE PERSPECTIVES

The comparison of two groups of patients with little in common (patients with epiphora and patients with cataract) may lead to several problems. However, the study described in Paper I shows that the impact of epiphora on activities of daily life is in parity with those experienced by patients awaiting cataract surgery on their second eye. While cataract surgery is seldom questioned in Western countries today, treatment for epiphora is less forthcoming.

Improved knowledge on the degree of visual disability in a group of patients is of importance for the allocation of health care resources and to ensure that effective treatment is available. The survey of current management strategies for lacrimal diseases (Paper II) showed that DCR is less available than CDCP, despite the fact that DCR has been demonstrated to have a very high success rate in numerous studies.[19, 21, 53-57, 61, 62] The lack of surgical resources and training in DCR may be two reasons why CDCP is favored for the treatment of ALDO in the Nordic countries, even in cases of NLDO, and occasionally post-infection or post-fracture. However, CDCP is an inadequate alternative for the treatment of NLDO, as shown in Paper III. CDCP may be considered in the case of suspected canalicular stenosis, especially if DCR is deemed unsuitable due to medical considerations, for example, if anticoagulant medication cannot be adjusted. The patient should nevertheless be informed of the high risk of failure, especially if multiple stenoses are found during the procedure.

The role of silicone stenting in conjunction with DCR surgery is the subject of debate, and the evidence in the literature is contradictory. A factor that has not been adequately investigated is the duration of intubation. The study presented in Paper IV shows that, in uncomplicated procedures, a very high long-term success rate is possible with a duration of only one week. This is also cost-effective for the health care sector and convenient for the patient as there is no need for a second routine follow-up visit. There may be an optimal duration of intubation to achieve the positive effects of stenting, while retaining the stent for a longer period may lead to negative effects. Further studies should be carried out to investigate the effects of the duration of intubation.

Finally, it was possible to identify the lacrimal sac and track the movements of the lateral wall during blinking using UHF ultrasound *in vivo* and under physiological conditions (Paper V). Movement in the horizontal plane was shown to be mainly in the anterior-posterior direction, i.e. parallel to the bone in the lacrimal sac fossa, indicating that previous theories regarding the lacrimal sac pump may need to be revised. A better understanding of the mechanisms behind the active drainage of tears would improve our understanding of functional epiphora and hopefully enable the development of better treatment.

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REFERENCES

1. Vagge A, Ferro Desideri L, Nucci P, et al. Congenital nasolacrimal duct obstruction (cnldo): A review. *Diseases*. 2018; 6.

2. Kanski JJ, Bowling B, Nischal KK.Pearson A. Clinical ophthalmology : A systematic approach. Edinburgh: Elsevier/Saunders; 2012.

3. Ayub M, Thale AB, Hedderich J, et al. The cavernous body of the human efferent tear ducts contributes to regulation of tear outflow. *Invest Ophthalmol Vis Sci*. 2003; 44: 4900-7.

4. Kakizaki H, Takahashi Y, Mito H.Nakamura Y. Movement of the lacrimal canalicular wall under intracanalicular pressure changes observed with dacryoendoscopy. *Ophthal Plast Reconstr Surg*. 2015; 31: 73-4.

5. Kakizaki H, Zako M, Miyaishi O, et al. The lacrimal canaliculus and sac bordered by the horner's muscle form the functional lacrimal drainage system. *Ophthalmology*. 2005; 112: 710-6.

6. Kakizaki H, Zako M, Nakano T, et al. The medial horn and capsulopalpebral fascia in the medial canthus are significant antagonists of the orbicularis oculi muscle for lacrimal drainage. *Ophthalmologica*. 2004; 218: 419-23.

7. Kang H, Takahashi Y, Nakano T, et al. Medial canthal support structures: The medial retinaculum: A review. *Ann Plast Surg*. 2015; 74: 508-14.

8. Shams PN, Verdick RE.Allen RC. In vivo demonstration of the lacrimal pump. *Ophthal Plast Reconstr Surg*. 2016; 32: e25.

9. Ali MJ, Zetzsche M, Scholz M, et al. New insights into the lacrimal pump. *Ocul Surf*. 2020.

10. Paulsen FP, Thale AB, Hallmann UJ, et al. The cavernous body of the human efferent tear ducts: Function in tear outflow mechanism. *Invest Ophthalmol Vis Sci*. 2000; 41: 965-70.

11. Thale A, Paulsen F, Rochels R.Tillmann B. Functional anatomy of the human efferent tear ducts: A new theory of tear outflow mechanism. *Graefes Arch Clin Exp Ophthalmol*. 1998; 236: 674-8.

12. Paulsen F, Hallmann U, Paulsen J.Thale A. Innervation of the cavernous body of the human efferent tear ducts and function in tear outflow mechanism. *J Anat*. 2000; 197 (Pt 2): 177-87.

13. Paulsen F, Thale A.Mentlein R. What happens to tears inside the efferent lacrimal passage? An animal experimental study. *Graefes Arch Clin Exp Ophthalmol*. 2000; 238: 496-9.

14. Paulsen F, Thale A, Kohla G, et al. Functional anatomy of human lacrimal duct epithelium. *Anat Embryol (Berl)*. 1998; 198: 1-12.

15. Park J, Kim J, Kim M.Baek S. Aquaporin expression in the lacrimal sac of patients with primary and functional nasolacrimal duct obstruction. *Br J Ophthalmol*. 2017; 101: 519-24.

16. Sahlin S.Chen E. Gravity, blink rate, and lacrimal drainage capacity. *Am J Ophthalmol*. 1997; 124: 758-64.

17. Woog JJ. The incidence of symptomatic acquired lacrimal outflow obstruction among residents of olmsted county, minnesota, 1976-2000 (an american ophthalmological society thesis). *Trans Am Ophthalmol Soc*. 2007; 105: 649-66.

18. Lee J, Lee HK, Lee H, et al. Epidemiology of oculoplastic and reconstructive surgeries performed by a single specialist with 15 years' experience at a tertiary center. *J Craniofac Surg*. 2015; 26: e308-11.

19. Tirakunwichcha S, Rengwanidchakul E, Asawaphureekorn S, et al. Incidence of acquired lacrimal drainage system obstruction in epiphoric patients in thailand. *Asian Biomedicine*. 2010; 4: 159-62.

20. Ali MJ, Psaltis AJ, Murphy J.Wormald PJ. Outcomes in primary powered endoscopic dacryocystorhinostomy: Comparison between experienced versus less experienced surgeons. *American journal of rhinology & allergy*. 2014; 28: 514-6.

21. Badhu B, Dulal S, Kumar S, et al. Epidemiology of chronic dacryocystitis and success rate of external dacryocystorhinostomy in nepal. *Orbit*. 2005; 24: 79-82.

22. Beshay N.Ghabrial R. Anatomical and subjective success rates of endonasal dacryocystorhinostomy over a seven-year period. *Eye (Lond)*. 2016; 30: 1458-61.

23. Kuchar A.Steinkogler FJ. Antegrade balloon dilatation of nasolacrimal duct obstruction in adults. *Br J Ophthalmol*. 2001; 85: 200-4.

24. Kafil-Hussain N.Khooshebah R. Clinical research, comparison of the subjective visual function in patients with epiphora and patients with second-eye cataract. *Orbit*. 2005; 24: 33-8.

25. Tasaki K, Hoshi S, Hiraoka T.Oshika T. Deterioration of contrast sensitivity in eyes with epiphora due to lacrimal passage obstruction. *PLoS One*. 2020; 15: e0233295.

26. Koh S, Inoue Y, Ochi S, et al. Quality of vision in eyes with epiphora undergoing lacrimal passage intubation. *Am J Ophthalmol*. 2017; 181: 71-78.

27. Shin JH, Kim YD, Woo KI, et al. Impact of epiphora on vision-related quality of life. *BMC Ophthalmol*. 2015; 15: 6.

28. Rose GE. The lacrimal paradox: Toward a greater understanding of success in lacrimal surgery. *Ophthal Plast Reconstr Surg*. 2004; 20: 262-5.

29. Taylor RS.Ashurst JV. Dacryocystitis. Statpearls. Treasure Island (FL); 2020.

30. Das AV, Rath S, Naik MN.Ali MJ. The incidence of lacrimal drainage disorders across a tertiary eye care network: Customization of an indigenously developed electronic medical record system-eyesmart. *Ophthalmic Plast Reconstr Surg*. 2018.

31. Linberg JV.McCormick SA. Primary acquired nasolacrimal duct obstruction. A clinicopathologic report and biopsy technique. *Ophthalmology*. 1986; 93: 1055-63.

32. Paulsen FP, Thale AB, Maune S.Tillmann BN. New insights into the pathophysiology of primary acquired dacryostenosis. *Ophthalmology*. 2001; 108: 2329-36.

33. Ali MJ.Paulsen F. Etiopathogenesis of primary acquired nasolacrimal duct obstruction: What we know and what we need to know. *Ophthalmic Plast Reconstr Surg*. 2019.

34. Curragh DS, Bassiouni A, Macias-Valle L, et al. The microbiome of the nasolacrimal system and its role in nasolacrimal duct obstruction. *Ophthalmic Plast Reconstr Surg*. 2020; 36: 80-85.

35. Ali MJ.Paulsen F. Prolactin and prolactin-inducible protein (pip) in the pathogenesis of primary acquired nasolacrimal duct obstruction (pando). *Med Hypotheses*. 2019; 125: 137-38.

36. Ali MJ.Paulsen F. Surfactant proteins: Role in lacrimal drainage disorders. *Med Hypotheses*. 2019; 124: 35-36.

37. Ali MJ, Bráuer L, Schicht M.Paulsen F. Altered surfactant protein expression in primary acquired nasolacrimal duct obstruction. *Ophthalmic Plast Reconstr Surg*. 2019; 35: 553-57.

38. Bartley GB. Acquired lacrimal drainage obstruction: An etiologic classification system, case reports, and a review of the literature. Part 1. *Ophthalmic Plast Reconstr Surg*. 1992; 8: 237-42.

39. Bartley GB. Acquired lacrimal drainage obstruction: An etiologic classification system, case reports, and a review of the literature. Part 2. *Ophthalmic Plast Reconstr Surg*. 1992; 8: 243-9.

40. Bartley GB. Acquired lacrimal drainage obstruction: An etiologic classification system, case reports, and a review of the literature. Part 3. *Ophthalmic Plast Reconstr Surg*. 1993; 9: 11-26.

41. Esmaeli B, Hidaji L, Adinin RB, et al. Blockage of the lacrimal drainage apparatus as a side effect of docetaxel therapy. *Cancer*. 2003; 98: 504-7.

42. Joganathan V, Patel BCK, Malhotra R.Norris JH. The kissing puncta: An under-reported and stubborn cause of epiphora. *Eye (Lond)*. 2019; 33: 505-08.

43. McNab AA. Lacrimal canalicular obstruction associated with topical ocular medication. *Aust N Z J Ophthalmol*. 1998; 26: 219-23.

44. Alkatan H.Al-Qurashi M. Is routine histopathological examination of dacryocystorhinostomy/dacryocystectomy specimens necessary? A tertiary eye hospital experience. *Can J Ophthalmol*. 2017; 52: 34-41.

45. Bewes T, Sacks R, Sacks PL, et al. Incidence of neoplasia in patients with unilateral epiphora. *J Laryngol Otol*. 2015; 129 Suppl 3: S53-7.

46. Sobel RK, Carter KD.Allen RC. Bilateral lacrimal drainage obstruction and its association with secondary causes. *Ophthalmic Plast Reconstr Surg*. 2014; 30: 152-6.

47. Cho WK, Paik JS.Yang SW. Surgical success rate comparison in functional nasolacrimal duct obstruction: Simple lacrimal stent versus endoscopic versus external dacryocystorhinostomy. *Eur Arch Otorhinolaryngol*. 2013; 270: 535-40.

48. Guercio B, Keyhani K.Weinberg DA. Snip punctoplasty offers little additive benefit to lower eyelid tightening in the treatment of pure lacrimal pump failure. *Orbit*. 2007; 26: 15-8.

49. Kielhorn I.Rowson NJ. Lateral canthal surgery in the management of epiphora. *Orbit*. 2002; 21: 111-6.

50. Narayanan K.Barnes EA. Epiphora with eyelid laxity. *Orbit*. 2005; 24: 201-3.

51. Simsek I, Yabas Kiziloglu O.Ziylan S. External dacryocystorhinostomy for the treatment of functional nasolacrimal drainage obstruction. *Turk J Ophthalmol*. 2015; 45: 208-12.

52. Tong NX, Zhao YY.Jin XM. Use of the crawford tube for symptomatic epiphora without nasolacrimal obstruction. *Int J Ophthalmol*. 2016; 9: 282-5.

53. Rosenstock T.Hurwitz JJ. Functional obstruction of the lacrimal drainage passages. *Can J Ophthalmol*. 1982; 17: 249-55.

54. Caglar C, Yener HI, Gul A.Ozcimen M. The modified technique of external dacryocystorhinostomy in the management of complicated nasolacrimal duct obstruction. *J Craniofac Surg*. 2016; 27: 416-9.

55. Dolman PJ. Comparison of external dacryocystorhinostomy with nonlaser endonasal dacryocystorhinostomy. *Ophthalmology*. 2003; 110: 78-84.

56. Lee MJ, Khwarg SI, Kim IH, et al. Surgical outcomes of external dacryocystorhinostomy and risk factors for functional failure: A 10-year experience. *Eye (Lond)*. 2017; 31: 691-97.

57. Mukhtar SA, Jamil AZ.Ali Z. Efficacy of external dacryocystorhinostomy (dcr) with and without mitomycin-c in chronic dacryocystitis. *J Coll Physicians Surg Pak*. 2014; 24: 732-5.

58. Tsirbas A, Davis G.Wormald PJ. Mechanical endonasal dacryocystorhinostomy versus external dacryocystorhinostomy. *Ophthal Plast Reconstr Surg*. 2004; 20: 50-6.

59. Boush GA, Lemke BN.Dortzbach RK. Results of endonasal laser-assisted dacryocystorhinostomy. *Ophthalmology*. 1994; 101: 955-9.

60. Mantynen J, Yoshitsugu M.Rautiainen M. Results of dacryocystorhinostomy in 96 patients. *Acta Otolaryngol Suppl*. 1997; 529: 187-9.

61. Sadiq SA, Ohrlich S, Jones NS.Downes RN. Endonasal laser dacryocystorhinostomy--medium term results. *Br J Ophthalmol*. 1997; 81: 1089-92.

62. Ciger E, Balci MK, Arslanoglu S.Eren E. Endoscopic-powered dacryocystorhinostomy without stenting: Long-term outcomes of 120 procedures. *American journal of rhinology & allergy*. 2018; 32: 303-09.

63. Tsirbas A.Wormald PJ. Mechanical endonasal dacryocystorhinostomy with mucosal flaps. *Br J Ophthalmol*. 2003; 87: 43-7.

64. Jo A, Lee SH, Song WC.Shin HJ. Effects of ostium granulomas and intralesional steroid injections on the surgical outcome in endoscopic dacryocystorhinostomy. *Graefes Arch Clin Exp Ophthalmol*. 2018; 256: 1993-2000.

65. Ali MJ, Psaltis AJ, Ali MH.Wormald PJ. Endoscopic assessment of the dacryocystorhinostomy ostium after powered endoscopic surgery: Behaviour beyond 4 weeks. *Clin Exp Ophthalmol*. 2015; 43: 152-5.

66. Sodhi PK, Pandey RM.Malik KP. Experience with bicanalicular intubation of the lacrimal drainage apparatus combined with conventional external dacryocystorhinostomy. *J Craniomaxillofac Surg*. 2003; 31: 187-90.

67. Rose GE. An interview with the authority. In: Hermda, RF; Fernandes, BB ed. Dacriologia aplicada: Sociedad Espanola de Chirugia Plastica Ocular y Orbitaria (SECPOO); 2018. p. 393-400.

68. Saiju R, Morse LJ, Weinberg D, et al. Prospective randomised comparison of external dacryocystorhinostomy with and without silicone intubation. *Br J Ophthalmol*. 2009; 93: 1220-2.

69. Kalin-Hajdu E, Cadet N.Boulos PR. Controversies of the lacrimal system. *Surv Ophthalmol*. 2016; 61: 309-13.

70. Ali MJ, Wormald PJ.Psaltis AJ. The dacryocystorhinostomy ostium granulomas: Classification, indications for treatment, management modalities and outcomes. *Orbit*. 2015; 34: 146-51.

71. Ing EB, Bedi H, Hussain A, et al. Meta-analysis of randomized controlled trials in dacryocystorhinostomy with and without silicone intubation. *Can J Ophthalmol*. 2018; 53: 466-70.

72. Unlu HH, Gunhan K, Baser EF.Songu M. Long-term results in endoscopic dacryocystorhinostomy: Is intubation really required? *Otolaryngol Head Neck Surg*. 2009; 140: 589-95.

73. Al-Qahtani AS. Primary endoscopic dacryocystorhinostomy with or without silicone tubing: A prospective randomized study. *American journal of rhinology & allergy*. 2012; 26: 332-4.

74. Chong KK, Lai FH, Ho M, et al. Randomized trial on silicone intubation in endoscopic mechanical dacryocystorhinostomy (send) for primary nasolacrimal duct obstruction. *Ophthalmology*. 2013; 120: 2139-45.

75. Fayers T.Dolman PJ. Bicanalicular silicone stents in endonasal dacryocystorhinostomy: Results of a randomized clinical trial. *Ophthalmology*. 2016; 123: 2255-9.

76. Goel R, Nagpal S, Kamal S, et al. Study of microbial growth on silicone tubes after transcanalicular laser-assisted dacryocystorhinostomy and correlation with patency. *Nepalese journal of ophthalmology : a biannual peer-reviewed academic journal of the Nepal Ophthalmic Society : NEPJOPH*. 2016; 8: 119-27.

77. Longari F, Dehgani Mobaraki P, Ricci AL, et al. Endoscopic dacryocystorhinostomy with and without silicone intubation: 4 years retrospective study. *Eur Arch Otorhinolaryngol*. 2016; 273: 2079-84.

78. Fayers T. External dacryocystorhinostomy with and without silicone intubation. *Br J Ophthalmol*. 2010; 94: 1267-8.

79. Sarode D, Bari DA, Cain AC, et al. The benefit of silicone stents in primary endonasal dacryocystorhinostomy: A systematic review and meta-analysis. *Clin Otolaryngol*. 2017; 42: 307-14.

80. Xie C, Zhang L, Liu Y, et al. Comparing the success rate of dacryocystorhinostomy with and without silicone intubation: A trial sequential analysis of randomized control trials. *Sci Rep*. 2017; 7: 1936.

81. Charalampidou S.Fulcher T. Does the timing of silicone tube removal following external dacryocystorhinostomy affect patients' symptoms? *Orbit*. 2009; 28: 115-9.

82. Keith CG. Intubation of the lacrimal passages. *Am J Ophthalmol*. 1968; 65: 70-4.

83. Napier ML, Armstrong DJ, McLoone SF.McLoone EM. Congenital nasolacrimal duct obstruction: Comparison of two different treatment algorithms. *J Pediatr Ophthalmol Strabismus*. 2016; 53: 285-91.

84. Connell PP, Fulcher TP, Chacko E, et al. Long term follow up of nasolacrimal intubation in adults. *Br J Ophthalmol*. 2006; 90: 435-6.

85. Fulcher T, O'Connor M.Moriarty P. Nasolacrimal intubation in adults. *Br J Ophthalmol*. 1998; 82: 1039-41.

86. Hussain RN, Kanani H.McMullan T. Use of mini-monoka stents for punctal/canalicular stenosis. *Br J Ophthalmol*. 2012; 96: 671-3.

87. Inatani M, Yamauchi T, Fukuchi M, et al. Direct silicone intubation using nunchaku-style tube (nst-dsi) to treat lacrimal passage obstruction. *Acta Ophthalmol Scand*. 2000; 78: 689-93.

88. Smith H, Lee R, Hawkes E.Khandwala M. Comment on: 'Use of mini-monoka stents for punctal/canalicular stenosis'. *Br J Ophthalmol*. 2012; 96: 1349.

89. Andalib D, Nabie R.Abbasi L. Silicone intubation for nasolacrimal duct stenosis in adults: Monocanalicular or bicanalicular intubation. *J Craniofac Surg*. 2014; 25: 1009-11.

90. Xu J, Hong J, Sun X, et al. Combined lacrimal passage probing and tobramycin/dexamethasone ophthalmic ointment infiltration: A minimally invasive surgical procedure for incomplete nasolacrimal duct obstruction. *Medicine (Baltimore)*. 2015; 94: e1483.

91. Bleyen I.Paridaens AD. Bicanalicular silicone intubation in acquired partial nasolacrimal duct obstruction. *Bull Soc Belge Ophtalmol*. 2008: 23-6.

92. Kashkouli MB, Kempster RC, Galloway GD.Beigi B. Monocanalicular versus bicanalicular silicone intubation for nasolacrimal duct stenosis in adults. *Ophthal Plast Reconstr Surg*. 2005; 21: 142-7.

93. Mimura M, Ueki M, Oku H, et al. Indications for and effects of nunchaku-style silicone tube intubation for primary acquired lacrimal drainage obstruction. *Jpn J Ophthalmol*. 2015; 59: 266-72.

94. Angrist RC.Dortzbach RK. Silicone intubation for partial and total nasolacrimal duct obstruction in adults. *Ophthal Plast Reconstr Surg*. 1985; 1: 51-4.

95. Ariturk N, Oge I, Oge F, et al. Silicone intubation for obstruction of the nasolacrimal duct in adults. *Acta Ophthalmol Scand*. 1999; 77: 481-2.

96. Delcoigne C.Hennekes R. Probing and silicone intubation of the lacrimal system in adults. *Bull Soc Belge Ophtalmol*. 1994; 254: 63-5.

97. Shah A, Tekriwal AK, Drummond PM.Woodruff G. Long-term results of closed nasolacrimal intubation in adults. *Eur J Ophthalmol*. 2007; 17: 490-3.

98. Baek JS, Lee S, Lee JH, et al. Predictors of silicone tube intubation success in patients with lacrimal drainage system stenosis. *Korean J Ophthalmol*. 2016; 30: 157-62.

99. Attas-Fox L.Codere F. Nonsurgical retrieval of retained lacrimal stenting material. *Ophthalmic Plast Reconstr Surg*. 2012; 28: 303-4.

100. Fayet B, Racy E, Ruban JM.Katowitz J. Pushed monocanalicular intubation. Pitfalls, deleterious side effects, and complications. *J Fr Ophtalmol*. 2011; 34: 597-607.

101. Mimura M, Ueki M, Oku H, et al. Evaluation of granulation tissue formation in lacrimal duct post silicone intubation and its successful management by injection of

prednisolone acetate ointment into the lacrimal duct. *Jpn J Ophthalmol*. 2016; 60: 280-5.

102. Rootman DS, Insler MS.Wolfley DE. Canaliculitis caused by mycobacterium chelonae after lacrimal intubation with silicone tubes. *Can J Ophthalmol*. 1989; 24: 221-2.

103. Bleyen I, van den Bosch WA, Bockholts D, et al. Silicone intubation with or without balloon dacryocystoplasty in acquired partial nasolacrimal duct obstruction. *Am J Ophthalmol*. 2007; 144: 776-80.

104. Diegelmann RF.Evans MC. Wound healing: An overview of acute, fibrotic and delayed healing. *Front Biosci*. 2004; 9: 283-9.

105. Sculean A, Gruber R.Bosshardt DD. Soft tissue wound healing around teeth and dental implants. *J Clin Periodontol*. 2014; 41 Suppl 15: S6-22.

106. Khoubian JF, Kikkawa DO.Gonnering RS. Trephination and silicone stent intubation for the treatment of canalicular obstruction: Effect of the level of obstruction. *Ophthalmic Plast Reconstr Surg*. 2006; 22: 248-52.

107. Yang SW, Park HY.Kikkawa DO. Ballooning canaliculoplasty after lacrimal trephination in monocanalicular and common canalicular obstruction. *Jpn J Ophthalmol*. 2008; 52: 444-49.

108. Liu D. A prospective randomized study of medications after silicone intubation. *Ophthalmic Surg Lasers*. 1996; 27: 434-7.

109. Liu D.Bosley TM. Silicone nasolacrimal intubation with mitomycin-c: A prospective, randomized, double-masked study. *Ophthalmology*. 2003; 110: 306-10.

110. Mimura M, Ueki M, Oku H, et al. Effect of rebamipide ophthalmic suspension on the success of lacrimal stent intubation. *Graefes Arch Clin Exp Ophthalmol*. 2016; 254: 385-9.

111. Hendry J, Chin A, Swan IR, et al. The glasgow benefit inventory: A systematic review of the use and value of an otorhinolaryngological generic patient-recorded outcome measure. *Clin Otolaryngol*. 2016; 41: 259-75.

112. Robinson K, Gatehouse S.Browning GG. Measuring patient benefit from otorhinolaryngological surgery and therapy. *Ann Otol Rhinol Laryngol*. 1996; 105: 415-22.

113. Feretis M, Newton JR, Ram B.Green F. Comparison of external and endonasal dacryocystorhinostomy. *J Laryngol Otol*. 2009; 123: 315-9.

114. Hii BW, McNab AA.Friebel JD. A comparison of external and endonasal dacryocystorhinostomy in regard to patient satisfaction and cost. *Orbit*. 2012; 31: 67-76.

115. Ho A, Sachidananda R, Carrie S.Neoh C. Quality of life assessment after non-laser endonasal dacryocystorhinostomy. *Clin Otolaryngol*. 2006; 31: 399-403.

116. Jutley G, Karim R, Joharatnam N, et al. Patient satisfaction following endoscopic endonasal dacryocystorhinostomy: A quality of life study. *Eye (Lond)*. 2013; 27: 1084-9.

117. Oh JR, Chang JH, Yoon JS.Jang SY. Change in quality of life of patients undergoing silicone stent intubation for nasolacrimal duct stenosis combined with dry eye syndrome. *Br J Ophthalmol*. 2015; 99: 1519-22.

118. Spielmann PM, Hathorn I, Ahsan F, et al. The impact of endonasal dacryocystorhinostomy (dcr), on patient health status as assessed by the glasgow benefit inventory. *Rhinology*. 2009; 47: 48-50.

119. Mistry N, Rockley TJ, Reynolds T.Hopkins C. Development and validation of a symptom questionnaire for recording outcomes in adult lacrimal surgery. *Rhinology*. 2011; 49: 538-45.

120. Ali MJ, Iram S, Ali MH.Naik MN. Assessing the outcomes of powered endoscopic dacryocystorhinostomy in adults using the lacrimal symptom (lac-q) questionnaire. *Ophthal Plast Reconstr Surg*. 2017; 33: 65-68.

121. Wong WK, Dean S.Nair S. Comparison between endoscopic and external dacryocystorhinostomy by using the lacrimal symptom questionnaire: A pilot study. *American journal of rhinology & allergy*. 2018; 32: 46-51.

122. Kabata Y, Goto S, Takahashi G.Tsuneoka H. Vision-related quality of life in patients undergoing silicone tube intubation for lacrimal passage obstructions. *Am J Ophthalmol*. 2011; 152: 147-50 e2.

123. Smirnov G, Tuomilehto H, Kokki H, et al. Symptom score questionnaire for nasolacrimal duct obstruction in adults--a novel tool to assess the outcome after endoscopic dacryocystorhinostomy. *Rhinology*. 2010; 48: 446-51.

124. Lundstrom M, Behndig A, Kugelberg M, et al. The outcome of cataract surgery measured with the catquest-9sf. *Acta Ophthalmol*. 2011; 89: 718-23.

125. Lundstrom M.Pesudovs K. Catquest-9sf patient outcomes questionnaire: Nine-item short-form rasch-scaled revision of the catquest questionnaire. *J Cataract Refract Surg*. 2009; 35: 504-13.

126. Sheikh R, Cinthio M, Dahlstrand U, et al. Clinical translation of a novel photoacoustic imaging system for examining the temporal artery. *IEEE Trans Ultrason Ferroelectr Freq Control*. 2019; 66: 472-80.

127. CM BTF. Applying the rasch model: Fundamental measurements in the human sciences. NJ, USA: Lawrence Erlbaum Associates, Inc., Publishers.; 2007.

128. Peter NM.Pearson AR. External dacryocystorhinostomy for the treatment of epiphora in patients with patent but non-functioning lacrimal systems. *Br J Ophthalmol*. 2010; 94: 233-5.

129. Sahlin S.Rose GE. Lacrimal drainage capacity and symptomatic improvement after dacryocystorhinostomy in adults presenting with patent lacrimal drainage systems. *Orbit*. 2001; 20: 173-79.

130. Moscato EE, Dolmetsch AM, Silkiss RZ.Seiff SR. Silicone intubation for the treatment of epiphora in adults with presumed functional nasolacrimal duct obstruction. *Ophthalmic Plast Reconstr Surg*. 2012; 28: 35-9.

131. Salour H, Khosravifard K, Bagheri A, et al. Efficacy of tightening of orbicularis oculi muscle in patients with functional nasolacrimal duct obstruction. *Orbit*. 2016; 35: 11-5.

132. Kumar GC, Kumar A, Nayak SR, et al. Morphology of the lacrimal sac and nasolacrimal duct in adult human cadaver. *Bratisl Lek Listy*. 2009; 110: 740-3.

133. Mito H, Takahashi Y, Nakano T, et al. Consecutive microscopic anatomical characteristics of the lacrimal sac and nasolacrimal duct: Cases with or without inflammation. *Invest Ophthalmol Vis Sci*. 2014; 55: 5233-7.

134. Takahashi Y, Suzuki T.Kakizaki H. Lacrimal sac movement under intrasac pressure changes observed with dacryoendoscopy. *Ophthalmic Plast Reconstr Surg*. 2014; 30: 313-4.

135. Machado MAC, Silva JAF, Garcia EA.Allemann N. Ultrasound parameters of normal lacrimal sac and chronic dacryocystitis. *Arq Bras Oftalmol*. 2017; 80: 172-75.

136. Pavlidis M, Stupp T, Grenzebach U, et al. Ultrasonic visualization of the effect of blinking on the lacrimal pump mechanism. *Graefes Arch Clin Exp Ophthalmol*. 2005; 243: 228-34.

137. Stupp T, Pavlidis M, Busse H.Thanos S. Presurgical and postsurgical ultrasound assessment of lacrimal drainage dysfunction. *Am J Ophthalmol*. 2004; 138: 764-71.

138. Tost FH, Darman J.Clemens S. 20-mhz ultrasound and its value in imaging of lacrimal plugs. *Ophthalmologica*. 2004; 218: 14-9.

139. Al-Faky YH. Anatomical utility of ultrasound biomicroscopy in the lacrimal drainage system. *Br J Ophthalmol*. 2011; 95: 1446-50.

140. Al-Faky YH. Physiological utility of ultrasound biomicroscopy in the lacrimal drainage system. *Br J Ophthalmol*. 2013; 97: 1325-9.

141. Espeit L.Lapole T. Effects of graduated compression stockings, local vibration and their combination on popliteal venous blood velocity. *Phlebology*. 2020: 268355520902000.

142. Sahlin S.Chen E. Evaluation of the lacrimal drainage function by the drop test. *Am J Ophthalmol*. 1996; 122: 701-8.

143. Kakizaki H, Takahashi Y, Miyazaki H.Nakamura Y. Movement of internal canalicular orifice in association with blinking: Direct observation after dacryocystorhinostomy. *Am J Ophthalmol*. 2013; 156: 1051-55.e1.